SEPTEMBER, 1947

BRAIN

VOL. 70, PART 3.

THE ANATOMY OF TRAUMATIC EPILEPSY.

BY

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THE cases of brain wound from the first World War were the subject of many studies with regard to the incidence of post-traumatic epilepsy. The anatomical position of the wounds was also considered, and a relatively high incidence of epilepsy was generally reported from mid-parietal wounds.

Between the two great wars, however, advances were made in the study of cortical physiology, which necessitate a new approach to the anatomy of traumatic epilepsy. The brilliant researches of Dusser de Barenne, McCullough and others, have demonstrated a close association between large areas of the sensorimotor cortex, and have investigated the functions of the cortical suppressor areas. They have found that stimulation of these suppressor bands relaxes existing muscular contraction and suppresses the motor response to stimulation of any motor focus of the sensorimotor cortex (McCullough, 1944).

The known suppressor bands in the chimpanzee as described by McCullough are shown in fig. 1. These workers have attempted to identify the suppressor bands with Brodmann's areas numbers 8, 4s, 2, 19 and 24, but according to Lashley and Clark (1946), these much-used cytoarchitectural divisions do not bear critical study. Hence the assumption that the position of suppressor bands in man can be calculated from cortical cytoarchitectonics is likely to be fallacious. Nevertheless the interleaving of important cortical regions by suppressor bands must clearly play a fundamental role in cerebral physiology, and this remarkable anatomical arrangement requires consideration in any study of the violent abnormality of cerebral physiology which is manifested in an epileptic convulsion.

The question naturally arises whether destruction of suppressor bands affects the subsequent liability to traumatic epilepsy, and whether in

operations to relieve traumatic fits there is any reason to suppose that suppressor bands should either be preserved or removed. The clinical study presented in this Paper consists of an attempt to plot the site of maximum brain damage in a large number of cases of gunshot wound of the cerebral hemisphere. This cannot be considered as a reliable method of investigating the problem, but the limited information it provides does suggest that the question requires further attention.

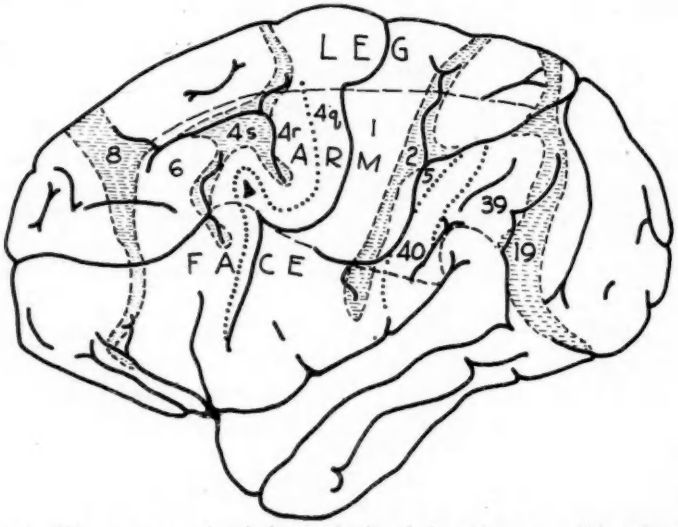

FIG. 1.—The suppressor bands in the brain of the chimpanzee (McCullough).

METHOD.

The material studied consists of 138 cases of brain wound followed by traumatic epilepsy with major convulsions, and 222 cases of brain wound with dural penetration but no epilepsy on a follow-up eighteen months to three years after wounding.

Patients with fits occurring within one month of wounding only are excluded, as also are those with focal fits which never led to a general convulsion.

The first step in this study is to choose a method of measurement for recording the site of the brain wound from X-rays of the skull. The nasion and inion can usually be identified with fair accuracy in the lateral radiogram and indeed the nasion-inion line seems to be the only practicable "base-line" to use. In each case therefore the skull X-rays were traced to show the site of the skull wound and of any intracranial fragments of bone or metal. X-rays taken before the original operation were used when available. An outline of a normal lateral skull X-ray was prepared to which the site of all the wounds could be transferred.

In order to transfer the site of wound from each X-ray tracing to this outline,

a line was drawn connecting nasion (N) and inion (I) and a perpendicular dropped from the centre of the skull defect (W) to meet NI at A—this line was prolonged upwards to meet the sagittal edge of the skull tracing at B (fig. 2).

In order to place the wound from each tracing on the prepared skull outline it is necessary first to find the position of A′ on the line N′ I′ (the "′" refers to the corresponding points on the skull outline on which the site of all the wounds is to be recorded), on the basis that the relation of AN to AI equals A′N′ to A′I′. Having determined the position of A′, A′B′ is drawn at right angles, and the position of W′ determined on the basis that AW : BW = A′W′ : B′W′. Fortunately this calculation can be carried out by a simple mechanical device which Dr. E. S. Schuster, *O.B.E.*, kindly devised and which is illustrated in fig. 3.

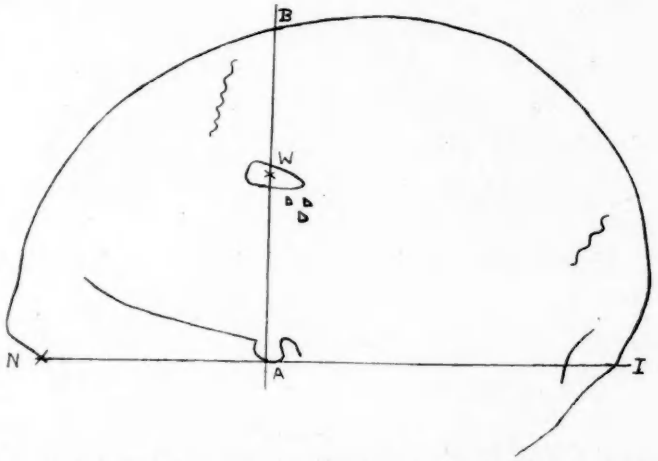

FIG. 2.—Method used for measuring the site of wounding from a tracing of the skull X-ray.

Fig. 4 gives the result of this procedure. Each X represents the centre of a brain wound which led to major epileptic fits in less than three years from the date of wounding. Owing to the great variation in the curve of the skull in the sagittal area, all wounds within 5 cm. of the mid-line are shown in the "halo" to the skull outline, in which the outer margin of the "halo" represents the mid-line. This distance is measured from the antero-posterior X-ray.

There must, of course, be inaccuracies in the placing of many of these X's for it is often necessary to measure from the centre of a post-operative skull defect which is not necessarily the point of maximum brain destruction. Wounds of all severities with or without infection, and to both sides of the head, are included in fig. 4, and some had retained pieces of metal

in the brain which were remote from the site of entry. Many of the patients had focal attacks in addition to the major convulsions.

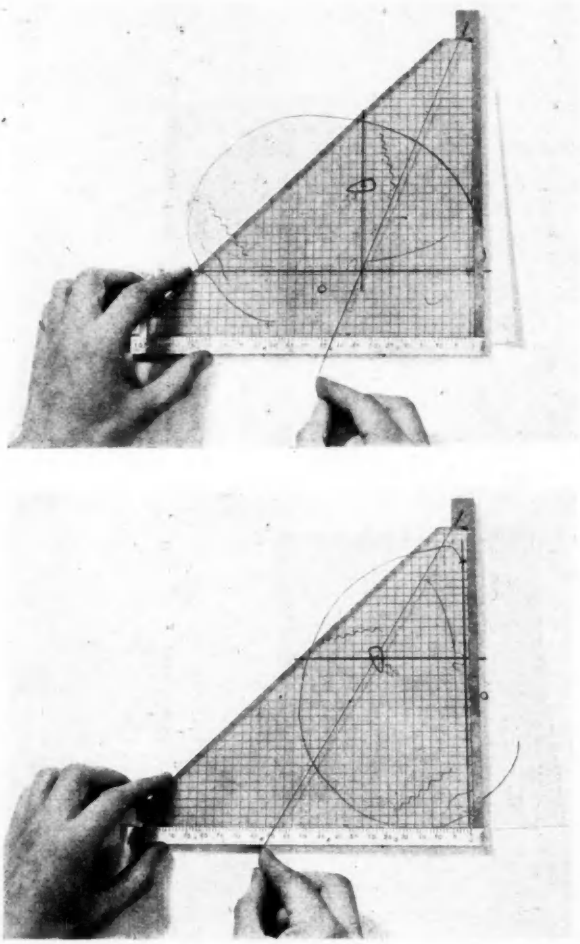

FIG. 3.—Apparatus for measuring the site of a brain wound from the X-ray tracing.

Examination of fig. 4 suggests a tendency for the X's both to congregate and also to shun certain regions. There is for example an accumulation

of X's just anterior to the coronal suture, and in a strip just posterior but parallel to the central sulcus. As the X's in fig. 4 include some cases

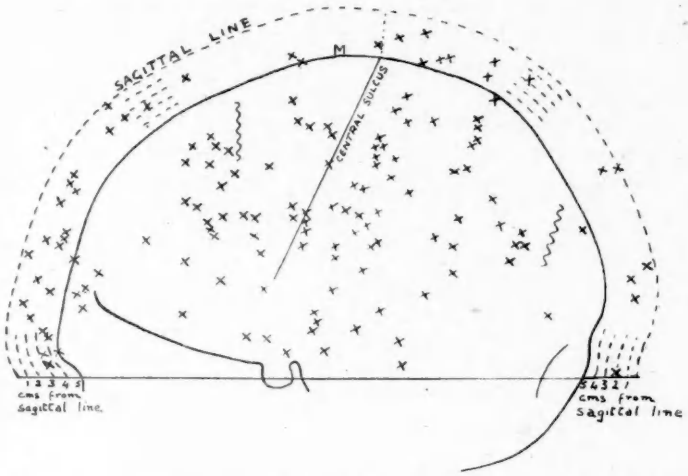

FIG. 4.—Each X represents the centre of a head wound which was followed by major epilepsy—all cases are shown. Wounds within 5 cm. of the sagittal line are shown in the halo.

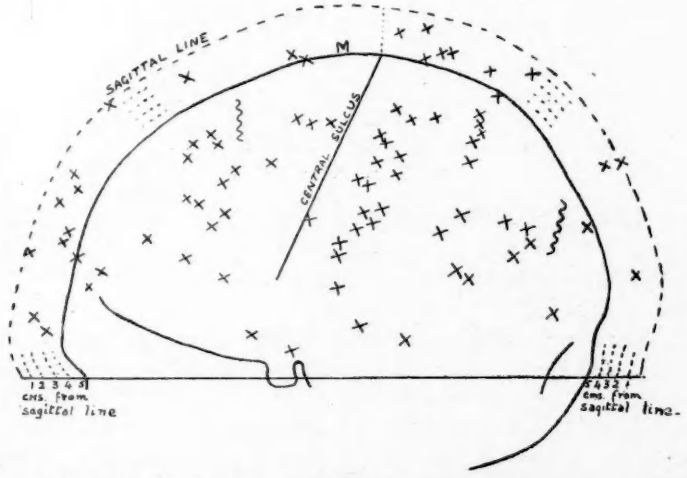

FIG. 5.—As for fig. 4, but local wounds without complications only are included.

in which the anatomical area of maximum damage is very extensive, an attempt has been made in fig. 5 to chart only those cases in which the brain wound was localized to one area, and was of limited extent and depth. All cases with brain infection, remote foreign bodies in the brain and with very deep or extensive injury to the brain have been excluded so that in fig. 5, therefore, the X's indicate with greater accuracy the area of maximum cortical and subcortical injury. The tendency for the X's to accumulate in zones is still evident in this figure.

In order to compare this distribution of X's with all wounds in this series which have not been followed by fits it would be necessary to chart

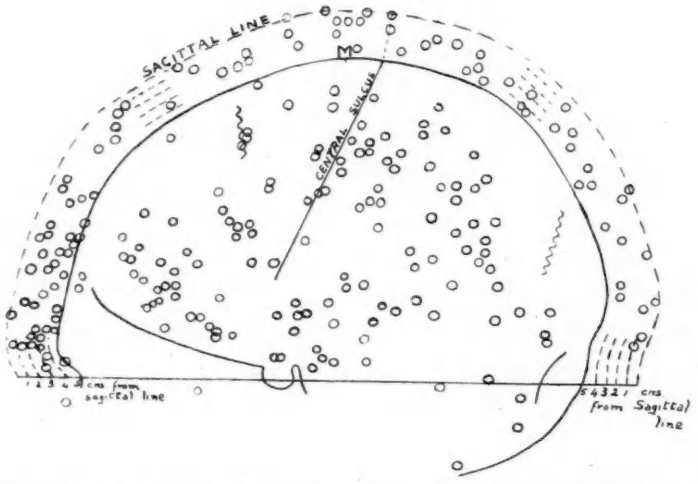

FIG. 6.—Each O represents the centre of a wound which was not followed by epilepsy.

about 700 wounds without epilepsy. This is not yet possible, but fig. 6 shows the position of the wound in 222 cases selected only in that the necessary X-rays and follow-up for eighteen months to three years after wounding were available. In fig. 6 each "O" represents the centre of the skull defect as do the X's in figs. 4 and 5. The distribution of O's in fig. 6 indicates that far from an accumulation of O's where the X's are numerous, there tend in some areas to be more O's where X's are scarce and fewer O's where X's are numerous. The accumulation of X's in certain zones is clearly not due to an excessive number of wounds to these areas.

In fig. 7 an attempt has been made to show the areas where the propor-

tion of X's is high and low. In zones III, V, and VII there is a high proportion of X's, this being most distinct in zone V. On the other hand in zones II, IV and VI the proportion of X's is much lower. In the parietal and Rolandic area it is particularly noticeable that the X's accumulate well behind the central sulcus, and indeed appear to shun the motor cortex. In this connection it must again be emphasized that the X's only include cases which have *major* fits, with or without focal fits. I have several records of cases with focal fits only in which the wound lies on or very near the Rolandic fissures, but these are not now considered further except to point out that the physiology and anatomy of the case with focal

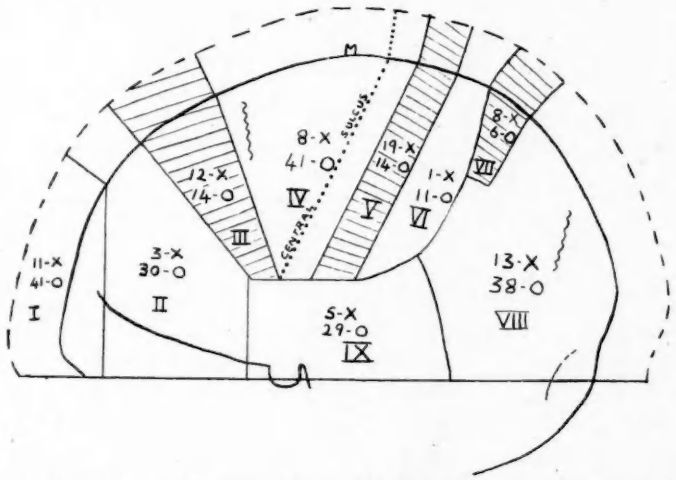

FIG. 7.—An arbitrary division of figs. 5 and 6 into 9 zones to show the relative proportion of X's and O's. The proportion of X's is high in the shaded zones.

fits only are not necessarily the same as of the case in which major convulsions occur.

The relationship of these wounds, if any, to suppressor bands cannot be established in a study such as this, but it may be noted that the zones with many X's tend to interleave with zones showing a low incidence of X's—an arrangement which is reminiscent of the arrangements of the suppressor bands as seen in fig. 1. Certainly the wounds falling into zones III, V, and VII are likely to have injured areas (Brodmann) 8, 2 and 18 respectively which are all suppressor areas. It is a matter of practical importance that this subject should be explored further, but it is doubtful

whether the method used in this study is sufficiently accurate to throw much further light on the problem. It is to be hoped, therefore, that neurosurgeons who have occasion to operate for traumatic epilepsy will take the opportunity to determine the site and extent of cortical brain damage with the greatest possible accuracy, and will make use of electrophysiological methods for this purpose.

The uncertainty surrounding the data presented is emphasized by the statistical study of the charts, and I am greatly indebted to Dr. R. B. Fisher for the following analysis:—

The data consist of location maps, on an approximate lateral plane projection of the cortex, of wounds causing fits ("positive" wounds) and wounds not causing fits ("negative" wounds). If these maps be divided into a set of arbitrary sub-areas, the proportions of positive and negative wounds in the sub-areas can be used to test whether there are specific macroscopic regions having the property that fits are caused only by wounds falling within them.

First, if there are no such regions, the proportion of positive wounds in the different sub-areas would be expected to differ from the mean proportion of positive wounds observed in the whole of the data only to the extent to be expected as the result of sampling variation. That is, the most frequent proportion of positive wounds would be expected to be close to the overall mean proportion, and other proportions of positive wounds would be expected to occur with frequencies which became smaller the further they deviated from the overall mean proportion. Since the factors determining this distribution are the chance ones of sampling it can be referred to as a "random" distribution.

On the other hand, on the hypothesis of macroscopic fit-producing regions, the proportion of positive wounds would be expected to be much higher than the overall mean in those sub-areas wholly or largely covering fit-producing regions, much lower than the overall mean in those sub-areas lying almost entirely outside a fit-producing area, and of the same order as the overall mean only when the sub-area covered appreciable amounts of both types of region. This frequency distribution would differ very considerably from the random distribution.

The χ^2 -test can be used to determine whether the frequency distribution departs significantly from the random distribution, and it has been so applied to data obtained by overlaying two different grids, of 2 cm. and 3 cm. side respectively, in two different orientations, over the location maps of figs. 4 and 5. All the tests indicate that the departure from

random distribution is no greater than could be produced by chance variation.

This test therefore provides no support for the occurrence of specific fit-producing regions, but it does not deny the possible truth of the hypothesis. It should be noted that, since all the wounds affect areas, whereas they are located at points on the maps, the effect will be that each sub-area as marked on the map will tend to include positive wounds due to effects produced in adjacent sub-areas. Further there can be no guarantee that all or even a rigidly fixed proportion of wounds falling in fit-producing regions will cause fits. Both these factors will tend to obscure any tendency of the frequency distribution to depart from the "random" distribution. The only justifiable conclusion is that any tendency for regional grouping of positive wounds is too small to show up in the face of obscuring factors.

Finally, it should be noted that the hypothesis that there exist certain cortical regions, trauma to which cannot produce fits, is statistically equivalent to the hypothesis of specific fit-producing regions, and is subject to all the considerations set out above.

Acknowledgments.

I am indebted to Dr. H. Steelman of the Montreal Neurological Institute for information regarding the position of the central sulcus in lateral X-ray films, also to Dr. R. Porter, Dr. C. W. M. Whitty, and Miss D. Martin-Hurst for help with the case records. The Medical Research Council provided secretarial assistance.

Summary.

(1) The site of injury in cases of brain wound has been charted in 138 cases of post-traumatic epilepsy, and in 222 cases which have not developed fits when followed up eighteen months to three years after wounding.

(2) The sites of wounding in the epileptic cases tend to accumulate in certain zones. The possibility that injury to suppressor areas may play a part in causing traumatic epilepsy is discussed.

(3) The need for exact anatomical studies at operation for post-traumatic epilepsy is stressed.

References.

Lashley, K. S., and Clark, G. (1946), *J. Comp. Neurol.*, **85**, 223.

McCullough, W. S. (1944), The Precentral Motor Cortex, edited by Paul C. Bucy, University of Illinois Press, Chapter 8.

DIFFUSE PROGRESSIVE METACHROMATIC LEUCOENCEPHALOPATHY:

A FORM OF SCHILDER'S DISEASE RELATED TO THE LIPOIDOSES.

BY

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In their classification of varieties of Schilder's disease Einarson and Neel (1938) drew attention to a form having as its distinctive pathological feature the presence in the cerebral white matter of a substance staining metachromatically with basic aniline dyes. The massive accumulation of this abnormal material, which stains bright pink in cresyl violet or toluidine blue preparations, readily differentiates cases of this "diffuse progressive metachromatic encephalopathy" from those varieties of diffuse sclerosis in which the chief product of myelin breakdown is neutral fat, and also from the rarer types characterized by prelipoid granules in the glial cells (Scholz, 1925) or by the appearance of mucinoid degeneration of the oligodendroglia (Greenfield, 1933).

The present example has been recorded because of certain unusual features, in particular the localization of metachromatic substance not only in the degenerating white matter of the brain but also in isolated groups of nerve cells and in some of the visceral organs. The condition thus reveals an affinity to amaurotic idiocy and the lipoidoses, a borderland of relationship recognized by several writers on the subject of Schilder's disease but seldom explored on account of the paucity of relevant pathological material.

Case Report.

E. M., a female, was admitted to Stoke Park Colony when 14 years 8 months old and died aged 18 years 1 month.

Family history.—The patient was the fourth of six children, four of whom the records describe as normal. An elder sister had died in another colony for mental defectives. Nothing is known of the grandparents or father who were dead at the time of E. M.'s admission to the colony. The mother, a school cleaner by occupation, stated during an interview at Stoke Park that she had been told, after the birth of her children, that her blood was "positive" and she had had a series of injections at that time.

Inquiries were made concerning the mentally defective sib and elicited the following information. The girl had been admitted to a colony for mental defectives

at the age of 15 years, having proved too low grade for a special school where she had been for a few months. She was described as an imbecile, childish in appearance, grimacing and putting out her tongue during conversation. She had no educational attainments, was doubly incontinent and needed every attention. Her weight was 6 stones, her height 4 feet 10 inches. A systematic medical examination revealed nothing of note, it being mentioned that there was no wasting or weakness in the limbs and that the gait and superficial and deep reflexes were normal. Her mental age was then 3 years 4 months as estimated by a Binet scale of tests. A year later it was noted that muscular rigidity was present in the legs and that the plantar reflexes were doubtfully extensor. Obvious mental and physical deterioration had occurred. Seven months later there was gross spastic rigidity affecting all limbs, though more marked in the legs. She had lost one stone in weight during the year and had become resistive, destructive, restless and dirty in habits. The terminal illness, which occurred when the patient was 17 years old, was rapid, status epilepticus with hyperpyrexia proving fatal in two hours. At the post-mortem examination the abnormal findings were: gross degeneration and vacuolization of the white matter of the cerebral hemispheres, most marked in the region of the left parietal lobe, congestion of the meninges with patchy chronic arachnoiditis, a small fibrotic gall bladder and cloudy swelling of the kidneys with a shimmering substance (? cholesterin) in the medullary pyramids.

History before admission to the colony.—The patient, E. M., began walking at 12 to 18 months and talking at about 2 years. The mother stated that the child had always been backward at school and had needed supervision in matters of dress and cleanliness. She had twice been knocked down by motor cars. She had been attending a special school for two years but was certified under the Mental Deficiency Acts when found to be incapable of receiving further educational benefit. On her fourteenth birthday she had a major epileptic fit and two other fits occurred in the following year.

Examination after admission.—At the age of 14 years 8 months the patient had a Binet mental age of 4 years 6 months and a Porteus mental age of 3 years 6 months. She was 5 feet 2 inches tall, weighed 6 st. 2 lb. and was of healthy appearance. Nothing abnormal was found on physical examination apart from rather brisk tendon-jerks and absent abdominal and plantar reflexes. The optic discs appeared somewhat flattened and the choroidal pigmentation was poor. The blood Wassermann reaction was singly positive. There were monthly major epileptic attacks despite phenobarbitone treatment. One year after admission a trace of albumen was found for the first time in the urine and this persisted. There were no casts. Her nurses had observed a slow physical and mental deterioration since admission. Eighteen months after admission the patient fell off her chair, fracturing the neck of each femur. It was considered likely that these were pathological fractures, since the trauma seemed minimal, but X-ray pictures revealed no coincident bone disease. Mental deterioration leading to profound dementia rapidly ensued and the possibility of juvenile general paralysis of the insane was considered. The cerebrospinal fluid, however, proved to be normal. She was now apparently blind but not deaf. Fits became more frequent and she became helpless, ataxic, flexed and rigid. Death occurred at the age of 18 years after a syncopal attack. She had been bedridden for twenty months.

Post-mortem examination.—The only visceral abnormality found was a very small gall bladder about the size of the little finger. On section, the wall was thickened and firm. The cavity was filled with a friable greyish mass adherent to the wall of the gall bladder in the region of the fundus.

Microscopic examination of visceral organs.—The gall bladder showed uniform fibrous thickening of its wall to a depth of about 1 mm. with here and there small collections of polymorphonuclear leucocytes. It was filled by a papillomatous growth. Many of the central cores of the papillomatous fronds were distended with aggregations of closely packed macrophage cells (fig. 1), the majority of which contained doubly refractile Scharlach staining material (cholesterol esters). When frozen sections embedded in gelatin were stained with cresyl fast violet or toluidine blue and differentiated in the usual way with Gothard's solution and absolute alcohol, groups of these macrophage cells were seen to contain a substance staining a metachromatic pink colour (fig. 2). This substance was not doubly refractile and resisted lipoid solvents for short periods. It was removed by embedding in paraffin.

The kidneys showed the picture of chronic glomerular nephritis with patchy areas of dense fibrosis associated with destruction of the tubules and a variety of glomerular damage ranging from shrinkage and increased cellularity of the glomerular tufts with fibrosis of Bowman's capsule to complete connective tissue obliteration of the glomeruli (fig. 3). Frozen sections stained with cresyl violet showed heavy deposits of metachromatic substance in the cortex (fig. 4). It was found chiefly in the areas of fibrosis, lying free in the tissue or in macrophage cells. It was also present within the tubular epithelium where it was sometimes mixed with doubly refractile lipoid, in which case the mixture stained a lighter pink colour. Numerous casts, sometimes partially or wholly tinged with the metachromatic hue, were seen in the larger tubules.

Other organs.—No metachromasia was observed in the liver cells but the walls of some of the larger intrahepatic bile ducts showed deposits. Metachromatic substance was absent from spleen, heart muscle and other organs examined. The suprarenals were poor in cortical lipoid and much colloid was present in the thyroid. The pars intermedia of the pituitary was relatively large but the gland as a whole showed no significant abnormality. The ovary was immature and hypoplastic.

Pathological Examination of the Nervous System.

Macroscopic.—The brain after fixation in formol saline weighed 880 grammes, of which cerebellum and attached brain stem accounted for 115 grammes. From the surface the hemispheres appeared normal but on coronal section an extensive greyish, gelatinous degeneration of the white matter was evident, the cerebral cortex and subcortical arcuate fibres remaining unaffected (figs. 5 and 6). These changes were roughly symmetrical in the hemispheres. The majority of the central cores of gyral white matter seemed to be partially preserved, the degeneration affecting mainly their basal and central parts. There was well marked dilation of the frontal horns of the lateral ventricles and also of the third ventricle, the thalami appearing shrunken (fig. 6). Greyish patches of degeneration were also visible in the white matter of each cerebellar hemisphere, not involving, however, the fields of the dentate nuclei.

Microscopic. Cerebral cortex.—Numerous representative blocks of tissue were examined by standard methods for nerve cells, axis cylinders, myelin, neuroglia and lipoid. The molecular layer of the cortex showed increased subpial gliosis and in many areas a generalized proliferation of fibrous astrocytes throughout its depth. In the grey matter the nerve cells were everywhere preserved and showed no significant pathological change. In the deepest part of the cortex, adjoining the subcortical arcuate fibres, there was a conspicuous increase of large astrocytes of fibrillary type, this change being more obvious in cortical regions immediately superjacent to areas

of white matter degeneration (fig. 11). As regards myelination, the radial fibres were well preserved, as were the striæ of Gennari, but the fibre systems of Baillarger were poorly defined. Coarsening and hypertrophy of the processes of the microglial cells was often observed in the deeper layers of the cortex (fig. 13), and throughout the grey matter of the left precentral gyrus these cells showed in cresyl violet preparations unipolar or bipolar flecks of pink metachromatic material. Oligodendroglia commonly showed swelling of the acute type.

Subcortical white matter.—The myelin sheaths of the arcuate fibres were preserved in all areas (figs. 7, 8 and 9), though in general the intensity of their staining was possibly somewhat reduced. They showed a heavy fibrillary gliosis (fig. 12) associated with an increase in number of astrocytic nuclei. Throughout the whole of the very extensive areas where the arcuate fibres formed the limits of the central gelatinous degeneration, this marginal zone was sharply defined by the presence of massive deposits of metachromatic substance, staining bright pink with basic aniline dyes (fig. 16). In most regions the metachromatic material appeared amid the fibres themselves but sometimes it was distributed in a thin granular band separating the lower surface of the arcuate fibres from the demyelinated subcortical white matter. The bulk of this substance was contained in large macrophage cells of the microglial series, the peripherally placed nuclei of which exhibited extreme crenation. Often the edges of such cells were vaguely defined, as though the contents had burst through the cell membrane, or as if more substance had been deposited upon their surfaces. In several areas quantities of this material appeared free in the tissues in the form of cloudy masses or confluent aggregations. In the central cores of gyral white matter and in the corpus callosum which was very thin, numerous isolated groups of metachromatic phagocytes were seen amid the myelinated fibres. In these situations, as one approached the central demyelinated region, a progressive failure of fibres to take up the hæmatoxylin of the myelin stain was evident, fibres gradually assuming the appearance of greyish tubes. Gross myelin beading was occasionally in evidence as were thickening, varicosities or end-bulb formation of axis cylinders. Fibrillary gliosis in the central cores was roughly proportional to the amount of myelin loss, but even in areas with preserved myelin there was often a conspicuous gliosis.

The centrum ovale, in areas of gelatinous change, showed almost complete demyelination (figs. 7, 8 and 9), only occasional poorly staining fibres being encountered, while rather more numerous naked axis cylinders were revealed in Gros-Bielschowsky preparations. Glial proliferation was present in the form of a loose fibrillary network. Relatively few microglial phagocytes were present in these degenerated areas and all contained the same rose-pink metachromatic material. In this central region aggregations of macrophages were often seen around the walls of blood-vessels though none containing neutral fat were encountered. Oligodendroglia cells had disappeared from the spongy areas but were demonstrated in regions containing myelinated fibres. In rare instances small round cell perivascular infiltrations were seen. Myelin islands or concentric structures were not features of this case.

Cerebellum.—The cerebellar cortex was normal. Myelin was preserved in the areas surrounding both dentate nuclei (fig. 14) but elsewhere the pathological changes were similar to those found in the centrum ovale of the cerebral hemisphere, the microglial mobilization being particularly intense. There was considerable fibrillary gliosis in the intact white matter and between the nerve cells of the dentate nuclei. Cresyl violet or toluidine blue staining of the *dentate nuclei* revealed striking abnormalities (figs. 15 and 16). Each nucleus was edged by a thin zone of

phagocytic microglia cells containing metachromatic material. The majority of the nerve cells exhibited gross swelling reminiscent of that seen in amaurotic idiocy with massive inclusions of metachromatic substance, the nucleus being usually displaced to one pole of the cell. These aggregations of pink staining granules were for the most part centrally placed in the nerve cell body, a rim of faintly staining cytoplasm remaining at the periphery. Rarely the whole cell body was filled, in which case the edge of the cell was formed by a condensed strand of displaced neurofibrils, as in amaurotic idiocy. Some swollen cells contained no such deposits, or only finely dispersed faintly staining granules. Scharlach R. stained these deposits a feeble yellowish-pink. With Nile blue sulphate a dark blue colour was produced while mucicarmine, osmic acid, the Kultschitsky-Pal method and impregnation with silver carbonate gave negative results. The substance was not doubly refractile.

Basal ganglia.—The medial parts of both thalami were atrophic, nerve cells and myelin being replaced by dense gliosis, scattered metachromatic phagocytes being present in the degenerated areas. The lateral nuclei also showed gliosis and considerable myelin loss. The anterior commissure, internal capsule and ansa lenticularis were feebly myelinated but were clearly marked out by enormous numbers of metachromatic phagocytes. The internal capsule showed marked gliosis and in addition to these microglial inclusions revealed conspicuous extra-cellular conglomerations of metachromatic granules following the axial course of the nerve fibres (figs. 18 and 20). Fine granules of metachromatic material were often seen in close proximity to nuclei of astrocytic type. In such areas of heavy gliosis and scanty myelin it was impossible to demonstrate oligodendroglia by impregnation methods. Each globus pallidus was uniformly poor in myelin and was crowded with metachromatic phagocytes, as were the compact fibre bundles of the putamina (fig. 17). Glial proliferation was conspicuous in all patially demyelinated areas. Both subthalamic nuclei exhibited the nerve cell swelling and metachromatic inclusions similar to those seen in the dentate nuclei (fig. 19).

Brain-stem.—The nerve cells of the oculomotor and trochlear nuclei were also affected by the amaurotic idiocy type of swelling and contained inclusions of the same character as have been described in the dentate and subthalamic nuclei (fig. 21). In the crura of the midbrain the fronto-pontine fibres were demyelinated and contained much metachromatic material. The pons appeared normal apart from scattered metachromasia in the transverse fibres and swelling associated with central chromatolysis of the cells of the nuclei pontis. The pyramidal tracts in the medulla were fully myelinated and no pathological change was found in the upper segments of the cervical spinal cord.

The optic nerves and chiasma appeared normal.

Solubility and staining properties of the metachromatic material.—The nerve cell inclusions lost their metachromatic quality with cresyl violet but still stained a blue colour with Nile blue sulphate after approximately twenty hours' immersion in acetone, ethyl alcohol, methyl alcohol, acid alcohol, ether and xylol. The granular contents of the microglial phagocytes after similar treatment retained their metachromatic quality and stained a bright purple or violet with Nile blue sulphate, in contrast to the plain blue inclusions of the nerve cells. Chloroform completely dissolved the microglial inclusions but not the nerve cell granules. Pyridine dissolved both as did embedding in xylol-paraffin. Substantially similar results were obtained with frozen sections of the kidney, though here a good deal of the fine metachromatic dusting in the tubular epithelium, where there was also admixture with doubly-refractile Scharlach staining lipoid, disappeared readily with all solvents.

Comment.

In the category of diffused progressive metachromatic leucoencephalopathy belong the cases of Alzheimer (1910), Witte (1921), Kaltenbach (1922), Carillo (1934), Einarson and Neel, Cases I and IV (1938), Van Bogaert and Dewulf (1939), Cardona (1939), Brandberg and Sjövall (1940) and Einarson and Neel, Case VIII (1940). The clinical features of these cases differed widely and only two of this series resembled the present example in being familial, namely that of Brandberg and Sjövall and of Cardona. In all members of this group widespread demyelination of the white matter of the brain was associated with extensive deposition of material staining metachromatically with basic aniline dyes. Kaltenbach (1922), an early writer on this subject, suggested two alternative explanations to account for the presence of this metachromatic substance. The first was that products originating from the breakdown of myelin had been arrested in an intermediate stage in their transformation to neutral fat owing to defective enzyme activity on the part of the scavenger cells. The second alternative was that the primary abnormality lay not in the phagocytes but in the constitution of the myelin sheath itself, the atypical degeneration products of which appeared in the glial scavenger cells as metachromatic bodies. The latter theory, implying as it does a process of abnormal myelination, introduces the wider conception of perverted lipoid metabolism and focuses attention upon the central mystery of Schilder's disease, the vulnerability of the myelin sheath. One or the other of these view-points, with minor modifications, has been adopted by subsequent writers on the subject, though Einarson and Neel (1940) regard a combination of both conceptions as necessary to a correct understanding of the pathogenesis of the condition.

The recorded cases of metachromatic leucoencephalopathy show considerable variation in their pathological findings, particularly as regards the type and intensity of the astrocytic response, the phagocytic activity of the microglia and the distribution of the metachromatic substance in relation to the areas of diffuse sclerosis. It is unnecessary to summarize here all such points of difference but some of the peculiar features of these cases may be mentioned in so far as they are relevant to the present discussion. Cardona (1939) found much metachromatic material situated at the periphery of degenerated areas, notably in the territory of the preserved arcuate fibres, and contained within large round cells identified by him as astrocytes. He described the microglia as inactive. In the present case, however, there can be little doubt that the large scavenger cells were microglial in origin and appropriate impregnation methods

showed transition forms between the larger cells and those of more usual dimensions. Further evidence of the activity of the microglia was furnished by the hyperplasia and metachromasia of some of the cortical elements and by the fact that most of the central demyelinated areas had been swept clear of degeneration products. The differences in solubility and staining reaction of the metachromatic granules of the phagocytes as compared with those in the affected nerve cells also suggests that the microglia had been capable of effecting some change in the chemical constitution of the ingested material.

The metachromatic inclusions found with remarkable symmetry in the dentate, subthalamic and mid-brain nuclei of the present case appear to be more massive than those reported by previous writers. The earliest reference to this rare finding is by Nissl (1910) who noted that metachromasia of glia and nerve cells might occur in diffuse sclerosis. Cardona (1939) described metachromatic granules in isolated cortical neurones and in some of the cranial nerve nuclei and anterior horn cells. Witte (1921) also observed similar inclusions but regarded the change as one affecting the lipochrome pigment. Van Bogaert and Dewulf (1939), commenting on this phenomenon, point out that after formalin fixation lipochrome may acquire metachromatic properties. This interpretation does not seem applicable to the present case since the solubility and staining properties of the substance (soluble in pyridine, unstained by osmic acid) did not resemble those of lipochrome. Moreover, normal lipochrome pigment was not seen in any nerve cell, even in such sites of predilection as the external geniculate bodies. It must also be emphasized that the inclusions occurred in grossly swollen nerve cells reminiscent of those found in amaurotic idiocy. This feature of the metachromatic variety of Schilder's disease is not the only link with amaurotic idiocy. Typical ballooning of nerve cells with prelipoid granules was observed in certain areas of the brain in one of Wicke's (1938) cases of diffuse sclerosis, and prelipoid granular accumulations in the glial cells similar to those of juvenile amaurotic idiocy have often been described in the familial juvenile variety of Schilder's disease. When one also takes into account the widespread arrest of myelination seen in the early cases of amaurotic idiocy and in Niemann-Pick's disease, an aplasia often combined, according to Bertrand and Von Bogaert (1934), with some degree of demyelination, a not unsubstantial foundation is laid for the belief that certain cases of Schilder's disease may belong pathogenetically to the group of lipoidoses. Such a belief would be strengthened if visceral changes indicative of disturbed lipoid metabolism were to be demonstrated in cases

of diffuse sclerosis and it may, therefore, be of importance that substantial deposits of metachromatic substance were found both in kidney and gall bladder in the present case. The literature affords only one other example of such combined cerebral and visceral involvement in Schilder's disease, namely, the case of Witte (1921), which may be briefly summarized here. A 42-year-old imbecile tramp died paralysed and demented after an illness lasting some years. The white matter of the cerebral hemispheres showed considerable loss of myelin with associated gliosis. All parts of the nervous system from frontal cortex to sacral cord exhibited in the white matter large quantities of metachromatic substance mainly within macrophage cells. Similar material was found in the cells of the anterior lobe of the pituitary, in the liver, testicles and tubular epithelium of the kidneys where "chronic parenchymatous nephritis" was present. The presence of metachromatically staining casts in the renal tubules suggested to the author the possibility of the condition being diagnosed during life. Witte considered that he was dealing with a disease of general metabolism, and though he provided no illustrations to his paper, it is clear that his case closely resembled the one recorded here. There is, however, an alternative to be examined before accepting the theory of a generalized metabolic disturbance. At first sight it might seem plausible to suppose that the metachromatic substance had been formed primarily in the brain and later, after absorption into the blood-stream, deposited elsewhere in the body. Certainly the metachromatic material appeared to be acceptable to the cerebral vessels without prior transformation into neutral fat, while its localization in the gall bladder and kidneys of the present case suggests an attempt at excretion, an attempt partially frustrated, perhaps, by the structural abnormalities of these organs. Moreover, chronic nephritis was also a feature of Witte's patient and until further cases of metachromatic leucoencephalopathy with visceral involvement are forthcoming it would perhaps be unwise to dismiss this association with glomerular damage as coincidental. However this may be, the weight of evidence strongly favours the view that this variety of Schilder's disease is a disorder of lipoid metabolism and the implication of the nerve cell bodies in the storage of metachromatic granules would be difficult to explain on any other basis. An analogous situation arises in the relationship of amaurotic family idiocy to the lipoidoses. On the one hand, there are the purely nervous cases of Tay-Sach's disease; on the other, Niemann-Pick's lipoidosis exemplifies the association of similar histological cerebral changes with extensive storage of sphyngomyelin elsewhere in the body, while intermediate between these two extremes are transitional

forms showing microscopical quantities of pre-lipoid material in the reticulo-endothelial cells of liver, spleen or lymph nodes. The reported cases of metachromatic leucoencephalopathy seem to fall naturally into a similar grouping. In the majority the abnormality lies solely in the white matter, a few cases showing in addition metachromatic inclusions in the nerve cells. Intermediate between these purely nervous forms and Witte's case comes the present example characterized by a more restricted visceral involvement. Although the reasoning is by analogy it seems permissible to deduce that a single pathogenetic principle is operative in all the members of this group and that both the cerebral and visceral abnormalities are expressions of an inherited lipoid dyscrasia.

According to Thannhauser (1940) the abnormal substance found in Niemann-Pick's disease is synthesized locally in the affected organs and is not deposited in them from the blood stream. This conception of a metabolic defect inherent in certain localized cellular elements is readily applicable to the pathology of metachromatic leucoencephalopathy and provides an explanation of the varied distribution of metachromasia in the cases under consideration.

Lack of precise knowledge as to the factors controlling the nutrition of the normal myelin sheath has necessarily delayed the unravelling of the pathogenesis of Schilder's disease and the well-known theory of primary oligodendroglial dysfunction in this condition rests upon slender and indirect evidence. In the present case, as in so many others, histological examination revealed merely that oligodendroglial cells had disappeared from areas of total myelin loss, that they were difficult to impregnate in areas of neuroglial sclerosis and that elsewhere they exhibited acute swelling, a commonplace and unspecific change. Nevertheless, if this metachromatic leucoencephalopathy belongs to the category of lipoidosis, as the findings of this case strongly suggest, it is necessary to postulate a functional derangement of cells concerned with myelin metabolism and it may well be that the metachromatic substance is the overt expression on the part of the interfascicular glia of such a derangement. It would follow that the linear aggregations of this material seen lying in the course of nerve fibres in the present case may be regarded as a consequence of an abnormal synthesis, not of myelin degeneration, though the substance is finally removed by microglial phagocytes. It may also be supposed that as the result of oligodendroglial dysfunction the myelin sheaths become progressively atrophied, eventually disappearing without the formation of neutral fat breakdown products usually found in more acute demyelinating processes. Such a conception is consistent with

the theory of pathogenesis formulated by Einarson and Neel (1940) who speak of "a constitutional morbid disposition of the factors regulating lipoid metabolism" and insist that the selective character of the white matter lesions in Schilder's disease must be attributed to implication of the interfascicular glia.

In conclusion, a few remaining points of interest may briefly be considered. Since congenital syphilis and trauma have been cited as possible precipitatory antecedents to Schilder's disease, it may be noted that both these doubtful ætiological factors occurred in this case. The association of the disease with previous mental defect has also been described by others. It is particularly unfortunate that no histological examination was made of the brain and organs of the affected sib, for although she undoubtedly suffered from Schilder's disease, it is uncertain whether this was of the metachromatic variety. It is noteworthy that in both cases small, fibrosed gall bladders were found and it is possible that this abnormality is genetically conditioned, but again, it is unknown whether a papilloma also occurred in the sister's malformed organ.

Summary.

Clinical and pathological details have been given of a female imbecile who died at the age of 18 years from Schilder's disease. The brain revealed advanced demyelination of the central white matter of cerebral and cerebellar hemispheres associated with extensive deposition of a substance staining metachromatically pink with cresyl violet. Similar material was found in grossly swollen nerve cells of dentate, subthalamic, oculomotor and trochlear nuclei of both sides of the brain. The kidneys showed chronic glomerular nephritis and considerable amounts of similar metachromatic substance were seen in the renal cortex, in the tubular epithelium and in occasional casts. Metachromatic material contained in macrophages was also present in the connective tissue stroma of a papillomatous growth that filled the small fibrotic gall bladder of this patient. An elder sister of the patient had died in another colony for mental defectives and in this case also the post-mortem examination revealed the combination of Schilder's disease and a small fibrosed gall bladder. It is concluded that this example of "diffuse progressive metachromatic leucoencephalopathy" has pathogenetic affinity to the lipoidoses and that the metachromatic substance is probably formed locally in the affected organs as the result of perverted lipoid metabolism.

Fig. 1

Fig. 3

Fig. 2

Fig. 4

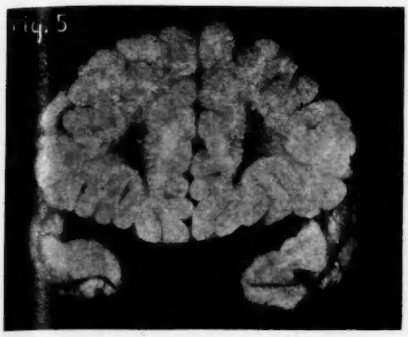


Fig. 5

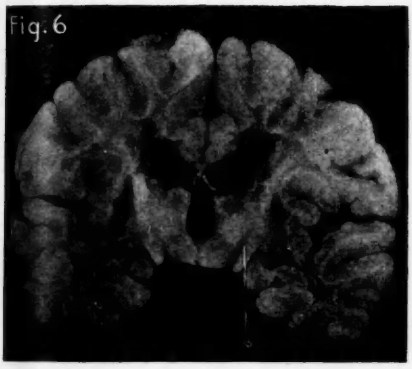
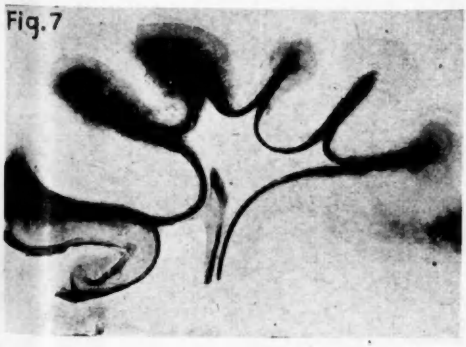


Fig. 6



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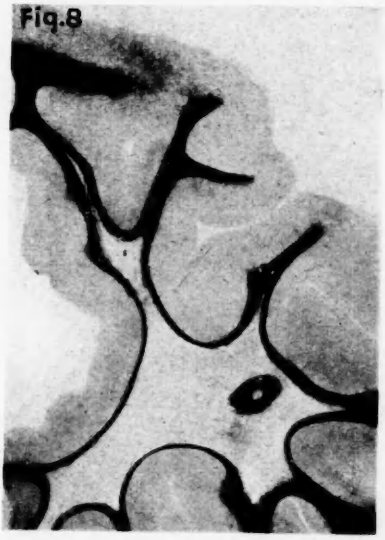

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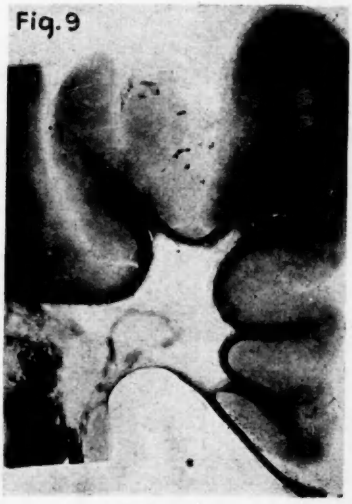

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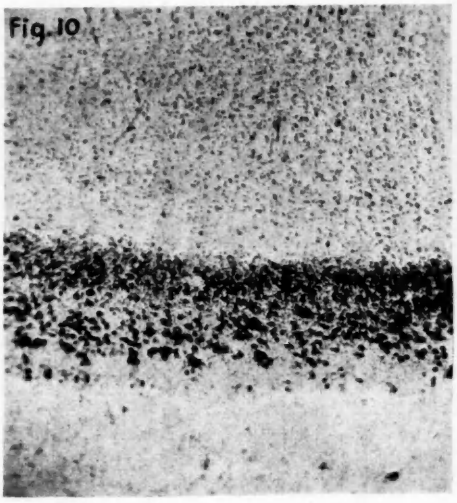
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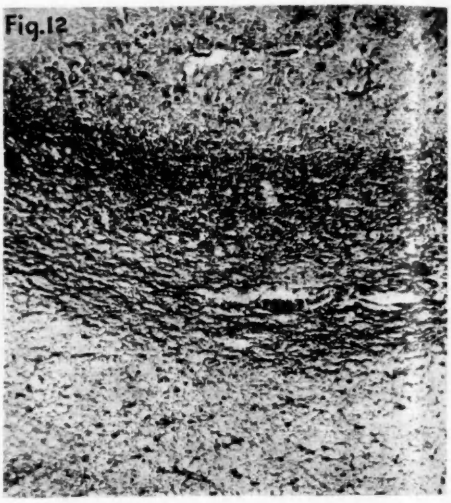
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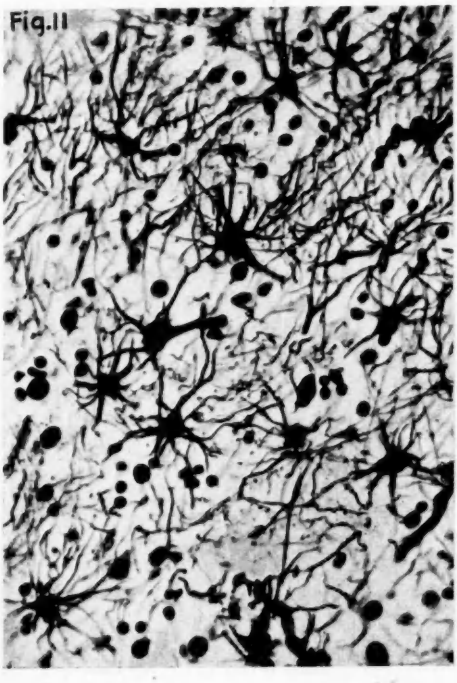
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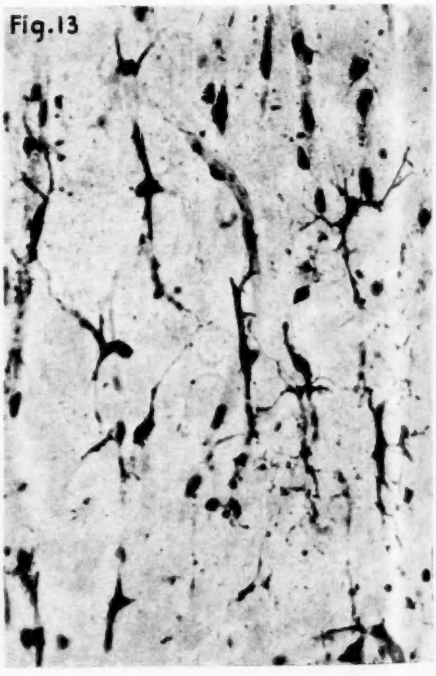
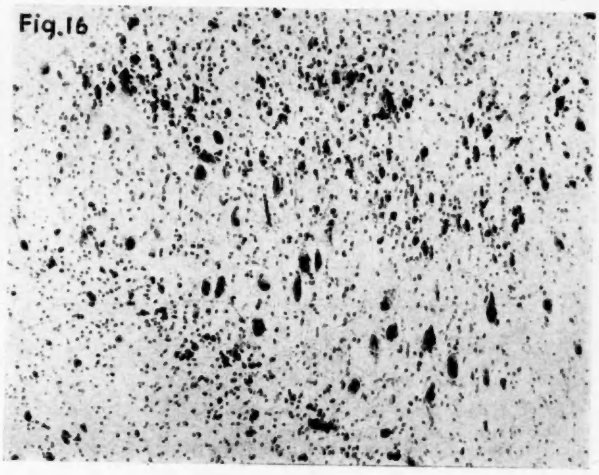


Fig. 13

Fig.14

Fig.16



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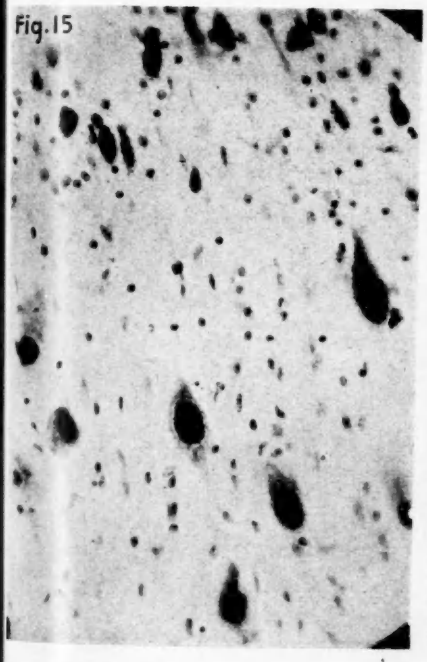
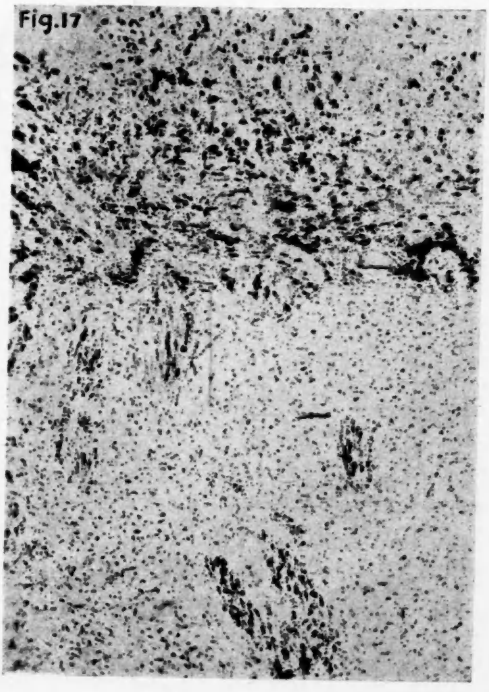


Fig.17



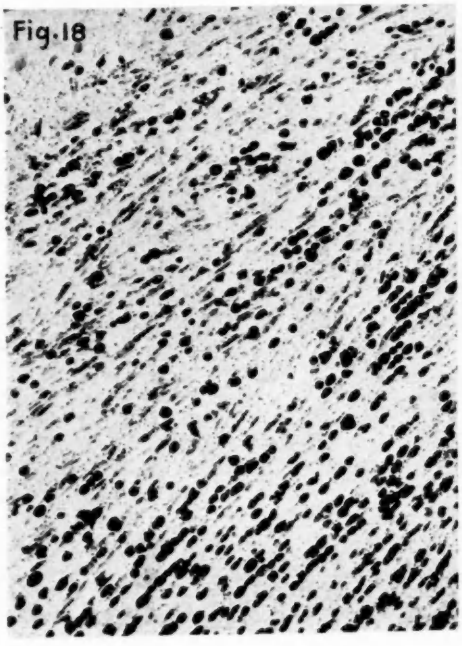


Fig. 18

Fig. 20

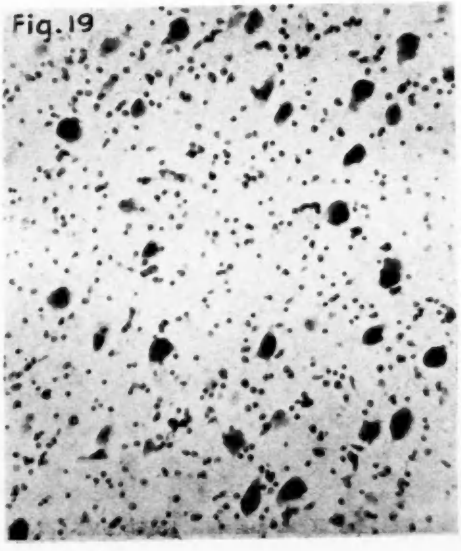


Fig. 19

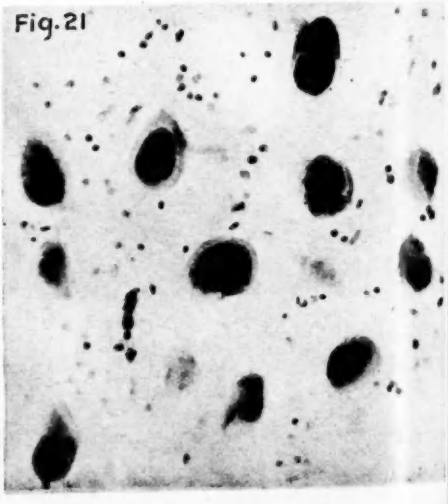


Fig. 21

EXPLANATION OF FIGURES.

FIG. 1.—Papilloma of the gall bladder. Note the macrophage cells distending the connective tissue cores of the tumour fronds. Mallory's connective tissue stain × 80.

FIG. 2.—As in fig. 1. Groups of macrophage cells containing metachromatic material appear black in the photograph. Cresyl violet × 80.

FIG. 3.—Kidney. Note the numerous shrunken and fibrosed glomeruli and much metachromatic substance (black in photograph) in the interstitial tissue. Cresyl violet × 80.

FIG. 4.—Kidney. Note two metachromatic casts in the centre of the field. The tubules (on the right) are outlined with metachromatic material. Cresyl violet × 180.

FIG. 5.—Coronal section through the frontal poles showing degeneration of the central white matter.

FIG. 6.—Coronal section through the thalami showing degeneration of the white matter, preservation of the arcuate fibres, atrophy of the thalami and dilatation of the lateral and third ventricles.

FIG. 7.—Temporal lobe showing degeneration of central white matter, preservation of arcuate fibres and the central cores of the gyri. Anderson's modification of the Kultschitsky-Pal method × 2.

FIG. 8.—Frontal pole. The apparent myelin island is in reality part of an adjacent gyrus. Stain and magnification as in fig. 7.

FIG. 9.—Central region of the cortex. Note the thin corpus callosum. Stain and magnification as in fig. 7.

FIG. 10.—Typical view of junction of cerebral cortex and centrum semi-ovale showing the area occupied by the arcuate fibres outlined by masses of metachromatic material. Cresyl violet × 36.

FIG. 11.—Gliosis in deepest part of the cerebral cortex. Hortega's method for astrocytes × 360.

FIG. 12.—Gliosis in the arcuate fibres. Mallory's phosphotungstic acid hæmatoxylin × 270.

FIG. 13.—Microglial proliferation in deepest layer of cortex. Penfield's method × 270.

FIG. 14.—Cerebellum. Note demyelination of central white matter beneath the field of the dentate nucleus. Anderson's modified Kultschitsky-Pal method × 2.

FIG. 15.—Dentate nucleus. The swollen nerve cells contain massive accumulation of metachromatic substance. Cresyl violet × 270.

FIG. 16.—Dentate nucleus. Metachromasia of nerve cells and microglial phagocytes. Cresyl violet × 80.

FIG. 17.—Basal ganglia. Macrophage cells containing metachromatic substance crowd the globus pallidus (above) and the compact fibre bundles of the putamen (below). Cresyl violet × 48.

FIG. 18.—Internal capsule. Note the numerous metachromatic phagocytes and also aggregations of metachromatic granules lying in the direction of the nerve fibres. Cresyl violet × 80.

FIG. 19.—Nucleus subthalamicus. Showing swelling and metachromasia of the nerve cells. Cresyl violet × 160.

FIG. 20.—As in fig. 18 × 280.

FIG. 21.—Trochlear nucleus. Swelling and metachromasia of nerve cells. Cresyl violet × 270.

REFERENCES.

ALZHEIMER, A. (1910), *Histologische und pathologische Arbeiten uber die Grosshirnrinde.* Jena, **3**, 9, 401.

BERTRAND, I., and VAN BOGAERT, L. (1934), *Encephale*, **29**, 505.

BOGAERT, L. VAN, and DEWULF, A. (1939), *Arch. Neurol. Psychiat., Chicago*, **42**, 1083.

BRANDBERG, O., and SJÖVALL, E. (1940), *Ztschr. f. Neurol.*, **170**, 131.

CARDONA, F. (1939), *Riv. di Pat. Nerv.*, **54**, 1.

CARILLO, R. (1934), *Sem. medica*, **41**, 938.

EINARSON, L., and NEEL, A. (1938), *Acta Jutland*, **10**, 2.

GREENFIELD, J. G. (1933), *J. Neurol. Psychopath.*, **13**, 289.

KALTENBACH, H. (1922), *Z. ges. Neurol. Psychiat.*, **75**, 138.

NISSL, F. (1910), *Enzyklopadie der microscopischen Technik, Berlin*, **2**, 284.

SCHOLZ, W. (1925), *Z. ges. Neurol. Psychiat.*, **99**, 651.

THANNHAUSER, S. J. (1940), "Lipidoses: diseases of cellular lipid metabolism." New York, p. 340.

WICKE, R. (1938), *Z. ges. Neurol. Psychiat.*, **162**, 741.

WITTE, F. (1921), *Munchen. med. Wchnschr.*, **68**, 69.

PENICILLIN IN SUPPURATIVE LESIONS OF THE BRAIN AND MENINGES.[1]

BY

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It is four years since my colleague Sir Howard Florey first gave us some penicillin for use in pyogenic infections of the brain and meninges. Supplies were scanty, but, as Florey and his colleagues (Abraham *et al.*, 1941) had shown that penicillin did not pass freely from the blood to the CSF and that it was not toxic when injected into the cisterna magna of the rabbit, we were in a position to investigate the local use of penicillin in these infections. The first preparations we used contained only 50 to 100 units of penicillin per mgm. and were thus very impure as compared with the crystalline preparation of penicillin II (1,650 units per mgm.) which we now use for all purposes. It is to some extent fortunate that our first therapeutic efforts were so largely influenced by shortage of supplies and by the impurity of the preparations, for we had to work out methods of using minimal effective doses of penicillin intrathecally (Cairns *et al.*, 1944). These methods have survived the advent of abundant supplies, though, as will be shown, the additional use of systemic penicillin in liberal doses is of considerable help in treatment.

Principles of Treatment.

I. *General theory.*—No one has questioned the notion that penicillin should be given access to all infecting organisms, but the limited powers of penicillin, however administered, to penetrate any large non-vascular area of infection may not at first have been fully appreciated. The dramatic success of the pioneer clinical trials of the Floreys (Florey and Florey, 1943) was with septicæmia and pyæmia, where the infective material was for the most part in finely particulate form in the blood stream and therefore easily accessible to circulating penicillin. In subacute bacterial endocarditis it proved more difficult to sterilize the infected valvular vegetations, and relapse after cessation of penicillin treatment was at first frequent.

[1] Delivered at a combined meeting of the Neurological Section of the Royal Society of Medicine and the Société de Neurologie de Paris on April 15, 1947.

Similarly, in treatment of pyogenic meningitis we found that a plaque of fibrino-purulent material, or a tiny abscess too small for surgical treatment, in the subarachnoid or ventricular spaces could reinfect the CSF once its penicillin content fell below bacteriostatic level. In one case of pneumococcal meningitis there were as many as 8 relapses in a period of 85 days (Smith *et al.*, 1946*a*, fig. 3).

In gunshot wounds of the brain also the question of access of penicillin to a contaminated or infected area was found to be of the first importance. It was no use placing penicillin in a brain wound and hoping that all infection would be quelled. Instead, it was necessary to remove all visible indriven matter and necrotic brain tissue: this procedure, as cultures and sections of débrided wounds have shown us, still leaves some bacteria and a microscopic layer of necrotic brain tissue lining the wound track, but this layer is so thin it can be penetrated by penicillin or, for that matter, by natural antibodies from the circulating blood.[1] Indeed, in war wounds in general the surgical procedures for penicillin treatment are precisely those which should be undertaken to encourage natural healing. When during the battle of Sicily penicillin was first introduced for the treatment of recent war wounds (Florey and Cairns, 1943) a cry was raised that this was an attempt to undermine the established surgical principle of débridement. In the event the effect was precisely opposite: penicillin immediately stimulated surgeons to a more meticulous performance. There was so much more to be gained, for penicillin did something which the tissue fluids and sulphonamides had never done with certainty: given adequate access to the wound it destroyed—or rather it assisted the natural bactericidal agents to destroy—*H. streptococcus, Staph. aureus,* and other sensitive organisms, and it enabled the surgeon to close débrided wounds early with a reasonable measure of safety—a procedure which, by diminishing the number of open wounds, inevitably diminished the risk of secondary infection in wards and operating theatres. In Oxford in 1944 we had over 350 brain wounds from Normandy and Belgium, and not a single case of β-hæmolytic streptococcal infection (Cairns, Calvert, Daniel and Northcroft, 1947).

This matter of access of penicillin to contaminating or infecting bacteria is momentous in all varieties of suppurative or potentially suppurative

[1] When Lister first used the deodorant carbolic acid, to prevent putrefaction in compound fractures of limbs, it was fortunate that he was dealing with accidental wounds. With missile wounds, with their much greater destruction of deep tissues, the trial must surely have failed without thorough excision of all the necrotic and infective material in the depths of the wound, a procedure only introduced fifty years later.

lesions. In the central nervous system its practical importance is seen not only in the treatment of brain wounds and abscesses but also in pyogenic meningitis, where blockage of the cerebrospinal pathways may interfere with the spread of penicillin injected intrathecally. For this reason it is essential when elaborating methods of chemotherapy, or when failing to obtain the expected cure, to control the methods of treatment by assay of the penicillin content of the CSF or other fluids at the seat of infection.

II. *Intrathecal penicillin.*—In diffuse infection of the cerebrospinal pathways due to susceptible organisms penicillin may be injected intrathecally into lumbar or cisternal subarachnoid space, or into the lateral ventricle. In the absence of blockage of the pathways penicillin spreads to all parts: thus, after injection by lumbar puncture it can be found in the ventricular fluid and in the cerebral subarachnoid spaces in adequate concentration within two to four hours (Cairns *et al.*, 1944).

Dosage.—A single intrathecal injection of 12,000 units will usually maintain an adequate concentration of penicillin in the CSF for twenty-four hours. The levels at the end of twenty-four hours usually vary between 0·03 and 0·6 units per c.c. but sometimes the penicillin disappears more rapidly. We believe that when it is essential to maintain an unbroken bacteriostatic concentration of penicillin in the CSF it is better to give intrathecal injections 12-hourly. Thus, in the first days of treatment of pneumococcal meningitis, before the results of penicillin assay are available, we give 12-hourly injections.

Increasing the dosage does not increase the persistence of penicillin in the CSF or the survival rate, if we may judge from the relatively low survival rate of Sweet *et al.* (1945) who gave daily doses up to 80,000 units intrathecally. The upper limit of intrathecal dosage of pure penicillin II has not yet been worked out, but there is plenty of experience to show that a large dose (50,000 to 100,000 units) of relatively pure penicillin intrathecally may cause severe meningeal reaction with blockage of the meninges, or damage to the cauda equina with retention of urine. Earl Walker and Johnson (1946) showed that pure penicillin when applied to the cerebral cortex in strong concentrations can produce fits. I wish therefore to emphasize the importance of moderate intrathecal dosage: large doses can do no good and may do harm. We have never exceeded 20,000 units at a single dose. Long-continued daily lumbar injections of even this dosage tend to depress the ankle-jerks, and thus presumably produce some damage of the cauda equina, though this is reversible.

Concentrations up to 5,000 units/c.c. normal saline may be used with-

out ill-effect. We usually employ a solution of 2,000 units/c.c. and dilute it with an equal quantity of CSF before injection.

Routes.—In most cases requiring intrathecal injection the lumbar route suffices, for if there is no obstruction by fibrin, adhesions, or foraminal herniations the whole of the cerebrospinal pathways can be supplied with an adequate concentration of penicillin by this means. But if the cerebrospinal pathways become blocked this route immediately becomes ineffective and recourse must be had to the cisternal or ventricular route. The cisternal route may be difficult in a patient with meningitis who is restless and has head retraction, and is inadvisable in patients with raised intracranial pressure and possible herniation of the cerebellar tonsils; also some blocks occur above the cisterna magna, notably in the aqueduct of Sylvius. Therefore, there should be no hesitation in using the ventricular route whenever a block is suspected, and every clinic which undertakes to treat meningitis should have facilities for urgent ventricular puncture. The most important early sign of blockage is that CSF ceases to flow freely at lumbar puncture. The method of testing the patency of the cerebrospinal pathway by studying the spread of penicillin has already been described (Smith *et al.*, 1946*a*). The ventricular route is also required when there is contamination of the ventricular pathways, e.g. from rupture of a cerebral abscess, or when the ventricle is opened during removal of a cerebral abscess.

III. *Subdural penicillin.*—Penicillin is required in the subdural space for treatment of purulent pachymeningitis and subdural abscess. The drug passes rapidly from the subdural space into the blood stream, as rapidly as from muscle (Smith *et al.*, 1946*a*), and consequently injections should be given every three to six hours. We have employed up to 10,000 units for each injection through an indwelling subdural catheter. Exceptionally, penicillin can disappear rapidly from the subarachnoid space by leakage into the subdural space. In one of our cases of pneumococcal meningitis (Smith *et al.*, 1946*a*, Case 8) penicillin escaped so rapidly from the subarachnoid space into a subdural hydroma that it was not possible to overcome the leptomeningitis until the subdural space had been obliterated by drainage of the hydroma.

IV. *Systemic penicillin.*—Penicillin given systemically does not pass into the cerebrospinal fluid in appreciable amounts. This is true both for animals and man (Abraham *et al.*, 1941; Cairns *et al.*, 1944; McDermott and Nelson, 1945). Some have claimed that when the meninges are inflamed more penicillin can pass from the blood to the CSF and they have argued that meningitis due to susceptible organisms, such as

pneumococcus, can be treated by systemic penicillin alone. Our observations do not confirm these claims and moreover we have seen a patient with recurring attacks of pneumococcal meningitis relapse while receiving systemic penicillin in full doses. Kinsman and d'Alonzo (1946) have effectively shown that systemic penicillin does not control meningococcal meningitis.

This does not mean that systemic penicillin should not be employed in pyogenic meningitis. On the contrary, it is of subsidiary value on several counts.

(1) It assists in overcoming the primary source of infection, such as otitis media, pneumonia, or frontal sinusitis; and also controls septicæmia, which may arise from the primary focus, or, as we have seen, from flare-up of the meningeal infection at a time when the primary source of infection has subsided.

(2) Penicillin systemically should assist in overcoming infection of the cerebral blood-vessels which may accompany purulent leptomeningitis. In pneumococcal meningitis the blood-vessels of the brain and meninges may show in the acute stage purulent endarteritis and thrombophlebitis, and in the subacute stage fibrinoid necrosis with or without foci of purulent panarteritis (Cairns and Russell, 1947). These lesions may produce multiple cerebral infarctions, with functional damage which persists after the infection has been overcome. We have seen these lesions in fatal cases of meningitis, and during successful treatment of meningitis have occasionally observed temporary clinical events which could be explained by focal areas of anoxia. From the striking absence of permanent sequelæ in our successful cases, we assume that an adequate concentration of penicillin in the circulating blood diminishes the likelihood of these lesions becoming irreversible.

(3) It is not known whether penicillin can pass from the blood stream into the perivascular spaces or the brain tissue. A few observations which we have made on the effects of systemic penicillin in bronchogenic cerebral abscess suggest that the spread of the abscess is to some extent controlled by the drug; for clinically these hitherto rapidly fatal lesions seem to develop less acutely than in the days before penicillin. If further experience confirms this view there is an additional reason for giving systemic penicillin in pneumococcal meningitis. For this condition is really a purulent meningo-encephalitis: in the parts of the brain nearest the surface or the ventricles necropsy studies have shown organisms, and, in and around the adjacent perivascular spaces, infiltration with polymorphonuclear leucocytes.

(4) Penicillin probably passes freely from the blood stream into the subdural space. In one of our cases one hour after intravenous injection of 25,000 units, we found a little fluid in the subdural space which contained 0·05 units/c.c. Systemic penicillin is therefore probably of value in purulent pachymeningitis.[1]

(5) Systemic penicillin is of value in all infections which involve the skull and scalp as well as the brain and meninges. Hence it should be given in purulent osteitis of the skull with intracranial extension of infection, and in all penetrating injuries of the brain showing superficial suppuration.

Crystalline penicillin II appears to be completely non-toxic when given by the systemic route. One patient, a man with actinomycotic abscesses

[1]Within twenty minutes of intramuscular injection of 200,000 units of penicillin the fluid of subdural hæmatomas contains 0·5 units/c.c.

of the peritoneal cavity and liver and bronchiectasis, from whom I removed a bronchogenic brain abscess, has had in the course of two years over 300,000,000 units of penicillin systemically in preparations of varying purity without severe reaction of any kind.[1]

Associated Sulphonamide Therapy.

In our first 16 cases of pneumococcal meningitis treated with intrathecal penicillin, sulphonamides were withheld in order to determine unequivocally the action of penicillin; there were 12 recoveries (Cairns *et al.*, 1944). Thereafter we have always combined sulphonamides by mouth with penicillin since the two drugs are not antagonistic and the pre-admission history of the majority of our cases has clearly shown the beneficial effect of sulphonamides. In adequate oral or systemic dosage these drugs, in particular sulphadiazine, usually control the symptoms of pneumococcal meningitis, at least for a time, even though they do not sterilize the CSF. It is our impression also that sulphonamides tend to prevent blockage of the cerebrospinal pathways in meningitis. Moreover sulphonamides by mouth pass readily into the CSF. The most important times to use sulphonamides are at the onset of meningitis, and again when the daily intrathecal injections of penicillin are being stopped.

Results of Treatment.

Table I summarizes our results to date in the use of penicillin in intracranial infections. In the early stages many of our cases were incompletely treated, owing to shortage of supplies, and we still occasionally see fulminating infections in which death occurs within twenty-four hours of admission, before penicillin has had a chance to overcome the infection. In all cases of meningitis early chemotherapy is important, and in acute cases should not wait upon a bacteriological diagnosis. For a variety of reasons we do not recommend that the general practitioner or neurologist should give intrathecal penicillin in the patient's home when he confirms his clinical suspicions by obtaining a turbid CSF on lumbar puncture. Certain organisms, and especially those of the coliform group, grow freely in penicillin and we believe that, save in exceptional circumstances, the risks of introducing unsusceptible organisms into the cerebrospinal pathways are too great to justify intrathecal injections of penicillin when

[1]As an illustration of the development of penicillin therapy with increase of supplies it is of interest to note that this patient has already had more than ten times the amount of penicillin used by the Royal Army Medical Corps on 300 wounded during the battle of Sicily (July and August, 1943).

TABLE I.—SUMMARY OF INTRACRANIAL INFECTIONS TREATED WITH PENICILLIN
(Excluding traumatic infections.)

	Total	*Incompletely treated*	*Died*		*Recovered*	*Remarks*
			of infection	*of other causes*		
Pneumococcal leptomeningitis	52	4	9	4	39	—
Streptococcal meningitis	12	—	7	—	5	Associated brain abscess 6
Staphylococcal meningitis	3	—	2	—	1	Associated brain abscess 2
H. influenza meningitis	5	—	3	2	3	—
Purulent pachymeningitis	15	6	9	—	6	—
Brain abscess :						
Thoracogenic	7	—	1	—	6	—
Others	26	3	6	1	19	—

scrupulous asepsis is impossible. In addition we have found that some varieties of meningitis tend to be associated with a clinically inconspicuous brain abscess: 6 of our 12 cases of streptococcal meningitis had an active brain abscess at the time when they came under treatment and the symptoms of abscess were masked by the meningitis (Smith *et al.*, 1946*b*). In such cases intrathecal injection of penicillin without immediate surgical treatment of the abscess merely precipitates death. The finding of streptococci in the CSF of a patient with meningitis calls for an immediate ventriculography unless there is clear evidence against the presence of cerebral abscess.

An additional reason for withholding intrathecal penicillin until a bacteriological diagnosis has been made is that some varieties of meningitis do not as a rule require intrathecal penicillin, e.g. meningococcal meningitis. We therefore recommend that the immediate treatment of a bacteriologically unidentified meningitis should be by systemic sulphonamides and systemic penicillin in full doses, with arrangements for continuing such treatment during transit of the patient to hospital.

Pneumococcal meningitis.—Our methods in this field have already been reported (Cairns *et al.*, 1944; Smith *et al.*, 1946*a*). As Table I shows, in 48 fully treated cases we have had only 4 deaths from infection:

4 other patients have died from other causes—traumatic fat embolism, hyploglycæmia, pneumonia and an unrecognized acute dilatation of the stomach—at a time when their meningitis was recovering. Of the patients who recover, about one-half pursue an uncomplicated course once they come under penicillin treatment, and the other half are subject to one or more relapses, presumed from collateral evidence to be due to the presence of a plaque of infected fibrino-purulent material in the subarachnoid or ventricular pathways. If these relapses are treated with the same promptness and persistence as the initial attack the patient will eventually make a complete recovery.

We have not yet seen a case of recurring pneumococcal meningitis in which the organism developed resistance to penicillin.

Meningococcal meningitis.—In this condition systemic and intrathecal penicillin may be required in the occasional case not responding satisfactorily on sulphonamides, in those with signs of impending renal block, or in those who become severely dehydrated from vomiting, especially children.

Purulent pachymeningitis.—Collection of pus, either free or loculated, in the subdural space, most commonly arise from acute or chronic infection of the paranasal sinuses associated with spreading osteomyelitis of the skull, and are usually due to anaerobic streptococcus or some other form of non-β-hæmolytic streptococcus. As the pus spreads in the subdural space the underlying cortex is paralysed and the common clinical picture is that of a progressive motor and sensory hemiplegia and homonymous hemianopia, combined with fever, œdema and great venous engorgement of the scalp. Leptomeningitis eventually ensues but is slight in the early stages. The infection is essentially one of the subdural space.

Dr. F. Schiller has analysed our material. Formerly our patients all died, but since penicillin has been freely available we have saved 6 of 9 patients. Bone infections require prolonged chemotherapy and as the skull is usually infected in these cases systemic penicillin should be continued for at least four weeks and often for longer. The dosage should be high, for anaerobic streptococci may be considerably less sensitive to penicillin than the common pyogenic organisms. If there are no obvious sequestra, removal of the infected parts of the skull may not be necessary. In the event of an associated leptomeningitis, subarachnoid or intraventricular penicillin may also be required.

One of the outstanding difficulties in purulent pachymeningitis is to prevent or to detect pockets of pus in various parts of the subdural space, and particularly on the medial surface of the cerebral hemisphere. With

increasing experience these difficulties should be overcome. I know of no type of infection of the nervous system in which a more profound change in prospect has been wrought by the advent of penicillin.

Brain abscess.—In most brain abscesses the causal bacteria are sensitive to penicillin and, as our figures indicate, the results of treatment of brain abscess have improved with the help of penicillin. This is particularly noticeable in the thoracogenic abscesses where, following the lead of Le Beau (1945, 1946), we have undertaken with success radical extirpation of the abscess in the acute stage. Hitherto this variety of abscess was almost invariably fatal because before the abscess could form the capsule necessary for its surgical removal the patient died from the combined effect of raised intracranial pressure and acute bronchopneumonia superimposed on his primary chest condition. With systemic penicillin the rapid clinical course of these metastatic brain abscesses seems to be slowed and the chest condition often held in check, while contamination of the brain during removal of the abscess can be counteracted by local and, if necessary, ventricular penicillin.

Cerebellar abscess has in the past presented a very difficult problem, not only because of the great danger of fatal medullary compression, but also because its removal almost invariably caused meningitis from contamination of the basal subarachnoid cisterns. Now, with the aid of penicillin, or, for coliform infections, streptomycin, these difficult abscesses can be radically removed with reasonable prospects of success. My colleague, Mr. J. B. Pennybacker, has removed a cerebellar abscess in five cases and all of these patients have recovered.

We have thus reached a stage in the treatment of brain abscess where the method of complete extirpation, which we owe to the classic work of Professor Clovis Vincent, has become standard for all varieties of brain abscess, with the exception of acute abscess after missile wound of the brain, and the rare chronic abscess which is deep-seated and better treated by repeated aspiration.

In those abscesses which are treated by preliminary aspiration and, for subsequent radiographic visualization, injection of thorotrast, we now also inject at each aspiration 10,000 to 20,000 units of penicillin in concentrated solution. Penicillin is not inactivated by thorotrast. A single injection does not necessarily sterilize an abscess due to susceptible organism(s). In a few cases where it seemed inadvisable to remove the abscess, treatment has been limited to repeated aspiration and penicillin injection, and the long-term result has been satisfactory. But we treated similar abscesses successfully by this method before we ever had any

penicillin. Though penicillin has greatly improved the prospects in certain types of brain abscess it has in no way diminished the need for unremitting expert care in each individual case.

Prevention of Infection of Operative Wounds.

Bacterial infection during operations has always been a bugbear to the neurosurgeon. Between 1927 and 1938 there were 23 deaths from infection in my series of 846 patients who had undergone 986 "clean" major neurosurgical operations (Cairns, 1939). At Oxford from 1939 onwards, with an air-conditioned theatre and other elaborate aseptic precautions, the incidence of infection was considerably reduced, notwithstanding one severe breakdown of sterilizing technique in 1940 during the emergency period after Dunkirk. However, post-operative sepsis was still interfering with our surgical efficiency. Therefore, in November, 1944, we decided to try the effect of penicillin as a prophylactic measure.

We used a powder of calcium penicillin mixed with sulphamezathine in the strength of 5,000 units per gramme. Sulphamezathine was employed as the vehicle because of its fine consistence, its solubility, its absence of epileptogenic effects (unlike sulphathiazole), and because, unlike sulphanilamide, it had no deteriorating effect upon the penicillin. At the conclusion of the operation all layers of the wound were frosted with this powder, approximately 1 to 3 grammes being used in each case. In most cases this gave a value of more than 0·02 units/c.c. penicillin in the wound juices for 12 to 18 hours, sufficient to inhibit the growth of the common pyogenic bacteria, and to inhibit partially other less sensitive bacteria. In addition, when the ventricular system or basal cisterns were widely opened we often injected into them a sterile solution of 10,000 units of penicillin in 5 c.c. of saline.

With several operators and many different types of neurosurgical operation it was not practical to set up controls. Therefore we decided to use this powder in every major intracranial and spinal operation and to compare the results obtained over a long period with those of earlier years during which, apart from the penicillin, conditions were for the most part identical.

The results of this experiment have recently been collected (Pennybacker *et al.*, 1947) and show a significant diminution of post-operative infection: in the pre-penicillin period (May, 1938, to November, 1944) in 1,169 "clean" major cerebral and spinal operations there were 51 infections of various kinds with 13 deaths, whereas with local application of penicillin-sulphamezathine powder to the wound in 670 similar operations there were 6 infections with no deaths. We conclude that insufflation with penicillin-sulphamezathine powder is a valuable additional measure against

bacterial infection at clean operations, and we would suggest that its applications may extend beyond the field of neurosurgery. We do not consider, however, that it has finally solved the problem of post-operative infection.

Conclusion.

Penicillin is not miraculous in its effects. Given access to sensitive organisms it will assist in their destruction only so long as its concentration remains adequate. But when penicillin has disappeared from the infected area organisms which remain can in certain circumstances multiply once more and attack the tissues with all their original virulence, as we have seen in relapsing meningitis. The use of penicillin therefore demands a greater degree of precision and systematic planning than has hitherto been accorded by the medical profession as a whole to less powerful remedies.

BIBLIOGRAPHY.

Abraham, E. P., Chain, E., Fletcher, C. M., Florey, H. W., Gardner, A. D., Heatley, N. G., and Jennings, M. A. (1941), *Lancet*, **2**, 177.

Le Beau, M. J. (1945), *Rev. Neurol.*, **11**, 331.

Le Beau, M. J. (1946), *J. Neurosurg*, **3**, 359.

Cairns, H. (1939), *Lancet*, **1**, 1193.

Cairns, H., Calvert, C. A., Daniel, P., and Northcroft, G. B. (1947), *Brit. J. Surg.* War Surgery Supplement No. 1.

Cairns, H., Duthie, E. S., Lewin, W. S., and Smith, H. V. (1944), *Lancet*, **1**, 655.

Cairns, H., and Russell, D. S. (1946), *J. Path and Bact.*, **58**, 649.

Florey, H. W., and Cairns, H. (1943), Investigation of War Wounds. Penicillin. A preliminary report to the War Office and the Medical Research Council. A.M.D. 7/90D/43.

Florey, M. E., and Florey, H. W. (1943), *Lancet*, **1**, 387.

Kinsman, J. M., and d'Alonzo, C. A. (1946), *New. Engl. J. Med.*, **234**, 459.

McDermott, W., and Nelson, R. A. (1945), *Amer. J. Syph.*, **29**, 403.

Pennybacker, J. B., Taylor, M., and Cairns, H. (1947), *Lancet*, **2**, 159.

Smith, H. V., Duthie, E. S., and Cairns, H. (1946*a*), *Lancet*, **1**, 185.

Smith, H. V., Schiller, F., and Cairns, H. (1946*b*), *Proc. Roy. Soc. Med.*, **39**, 613.

Sweet, L. K., Dumoff-Stanley, E., Dowling, H. F., and Lepper, M. H. (1945), *J. Amer. Med. Ass.*, **127**, 263.

Walker, E. A., and Johnson, H. C. (1946), "Penicillin in Neurology." C. C. Thomas, Springfield, Ill.

MUSCLE TONE AND THE ORGANIZATION OF THE MOTOR CORTEX[1]

BY

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In a previous paper (Bosma and Gellhorn, 1946) it was noted that tone in various muscles as indicated by the appearance of action potentials without cortical or reflex stimulation may be inhibited by weak cortical stimuli and that with increasing intensity of stimulation the inhibitory phase may be followed by a period of excitation leading to active contraction of the previously tonic muscles. These experiments served also as a means of studying the relation of reciprocal innervation to co-innervation (co-contraction). However, since no attempt had been made in the earlier work to investigate the question as to whether the tone of a certain muscle influences the reactivity of foci of the motor cortex, this and some related problems have been subjected to an experimental analysis.

The experimental work was performed on seven monkeys showing spontaneous tone in one or more muscles. The cortex was stimulated with condenser discharges for ten seconds. The EMGs were recorded with a 4-channel inkwriting crystograph (Offner). Details of the technique are found in the preceding paper. All records read from left to right.

Results.

(1) *Variations in tone as the result of cortical stimulation.*—It has been observed frequently that the tone of muscles may be inhibited by weak cortical stimulation. Fig. 1 gives an example of inhibition of the tone of the triceps on stimulation at threshold of a focus in the triceps area. If a point is stimulated in the central zone of area 4 from which the biphasic response[2] is commonly elicited, the triceps tone may not only be inhibited but, during this inhibitory period, a part of the biceps complex may also

[1] Aided by a grant from the National Foundation for Infantile Paralysis, Inc.

[2] The biphasic response, as described in the preceding paper, consists of a triceps-flexor carpi response followed by a biceps-extensor carpi activity and less commonly, of the opposite sequence.

appear as is seen in fig. 2 in the EMG[1] of the extensor carpi. That the activity was restricted to this part of the biceps complex and did not involve the biceps itself is well explained by the fact that in this zone the movers of the wrist are sometimes more prominently represented than

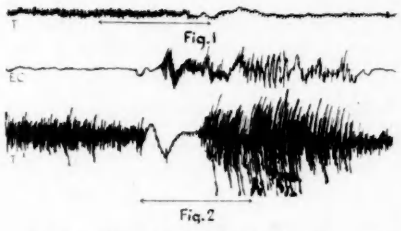

FIG. 1.—Monkey. Stimulation at site 24[2] with 5·3 v. (frequency 90/sec.) for 10 seconds, as indicated by the arrow. In this and the subsequent figures the following abbreviations are used: T = Triceps; B = Biceps; EC = Extensor Carpi radialis; FC = Flexor Carpi radialis; H = Hamstring.

FIG. 2.—Monkey. Site 35; 2·9 v.

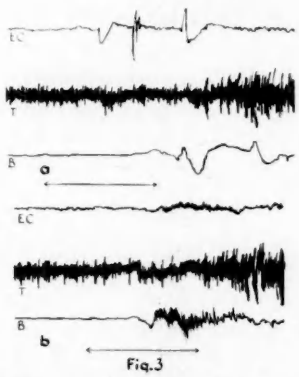

FIG. 3.—Monkey. Site 9; a = 3·6 v.; b = 4·3 v.

the muscles of the upper arm. Closer inspection of this figure shows that the inhibition of the tone of the triceps muscle ceases before the end of the stimulatory period and is followed by a distinct rebound of triceps activity. During this time the activity of the extensor carpi is reciprocally diminished.

[1]The EMG records of biceps and flexor carpi omitted, they showed no activity.
[2]Compare fig. 1 of the preceding paper for the location of the cortical sites stimulated.

These experiments are supplemented by the observations of fig. 3, based on the study of another monkey which likewise showed an extensor tonus. Stimulation of a flexor site was performed with 3·6 v (threshold) and 4·3 v. It is noted that the threshold stimulus did not alter the tone during stimulation but caused an intensification of it after the cessation of the stimulation (fig. 3a). As a stimulus of increased intensity is applied, the tone diminishes very slightly during the stimulation as the biceps complex is activated. In the experiment illustrated in fig. 3b, the activity of the extensor carpi is weak owing to the fact that a point far lateral in area 4 is stimulated but the response is strong enough to demonstrate that the activity of the whole biceps complex is related to a period of slight inhibition of the tone in the triceps. Following the end of stimulation the activity ceases in the biceps complex and the tone increases markedly in the triceps.

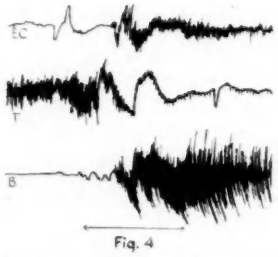

FIG. 4.—Monkey. Site 7; 2·9 v.

Whereas the tonic activity of the triceps was inhibited only temporarily by stimulation of a biceps point in the experiments of figs. 2 and 3 a more prolonged inhibitory effect is illustrated in fig. 4 following stimulation of another biceps focus. Since in this experiment stimulation of a biceps point close to its threshold abolishes the tone of the triceps not only for the period of stimulation but also for about 17 seconds thereafter, reciprocal innervation coinciding with the total period of inhibition of the tone of the triceps is demonstrated. The fact that the activity of the biceps complex continues as an after-discharge suggests that it is probably responsible for the delayed reappearance of the tone of the triceps muscle.[1]

It should, however, be noted that occasionally the tone of the triceps is not altered when stimulation of a flexor point elicits distinct activity in the biceps, as shown in fig. 5. Such results were obtained not only

[1] The reappearance of the triceps tone is not shown in the figure.

with threshold but also with slightly stronger stimuli. For example, in the same animal a result similar to that depicted in this figure was recorded when the intensity of stimulation was raised to 3·3 volts.

(2) *Muscle tone and muscular co-ordination.*—Tonic innervation of the triceps produces, in addition, some unexpected effects. It was seen in several animals that the tonic triceps muscle is not co-innervated with the biceps muscle on stimulation of prehension sites from which this phenomenon is distinctly elicited in non-tonic animals. Further observations suggest that the tonic activity in a muscle alters its responsiveness to cortical stimulation for some time. Thus co-innervation may be absent in a triceps muscle even after its tonic activity has disappeared. However, if an adequate period of time has passed, the behaviour of the EMG may revert to the normal pattern. Thus, in a monkey studied on two days, it was found that the tonic monkey failed to show co-innervation on the

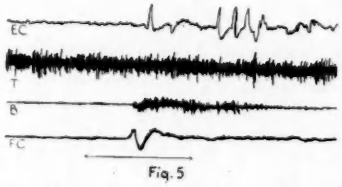

FIG. 5.—Monkey. Site 8; 2·9 v. (threshold).

first day but that on the second day in which tone was absent, typical co-innervation was restored.

Observations on a monkey which showed a tone in the biceps throw further light on the role of tone in cortically induced movements. The tonic innervation was present intermittently in this experiment disappearing at times as the result of cortical stimulation, for periods of varying duration. However, even in the absence of tone, the monkey showed unusual reactivity of the biceps muscle under conditions of cortical stimulation.

The EMGs of fig. 6a show that during stimulation of a focus close to the midline the biceps muscle is briefly activated in addition to the typical hamstrings-triceps response. In the following observation (fig. 6b) made after an interval of twelve minutes the contraction of the hamstrings is associated with activity of the biceps muscle, whereas the triceps record remains practically silent except for a slight after-discharge which occurs during the intervals separating the individual clonic discharges of the biceps muscle. A last test performed three minutes later (fig. 6c) was

taken while clonic activity occurred in the biceps prior to stimulation. The stimulus caused a typical contraction of the hamstrings. At the onset of this contraction the clonic activity of the biceps was inhibited. Thereafter there occurred in this muscle a period of tetanic contraction followed by clonic activity during which the contraction of the hamstrings continued while the triceps remained silent. Only after cessation of the

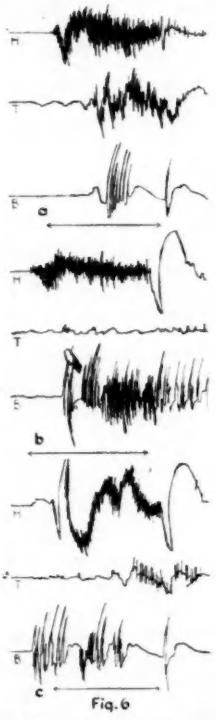

FIG. 6.—Monkey Site 33; a, b and c = 7 v.

clonic activity of the biceps does there appear a slight activity in the triceps muscle which continues for a few seconds as after-discharge.

These observations show that in an animal having periods of spontaneous biceps activity, fundamental alterations in the cortical response occur, in that the biceps muscle has the tendency to be activated from a cortical zone which does not have this effect in animals without spontaneous tone. However, under favourable conditions the typical pattern which is obtained from similar sites in non-tonic monkeys may be dis-

cerned in the tonic monkey in spite of some modifications. This is indicated by fig. 7, in which a slightly more lateral focus of the progression area was stimulated with 7 volts. In the first record the biceps shows spontaneous activity which at first proceeds unchanged when as the result of the cortical stimulation the hamstrings contract. A little later action potentials appears in the triceps and at their onset the biceps activity is temporarily inhibited. This period is followed by one in which, in spite of continuing slight activity of the triceps, a marked contraction of the biceps occurs. This record suggests that when the hamstrings-triceps complex (i.e. the progression pattern) is evoked an inhibitory influence is exerted from the centre associated with the activation of the triceps which holds the biceps in abeyance. If the "biceps" centre[1] is hyper-excitable, as indicated by spontaneous activity of this muscle, this inhibi-

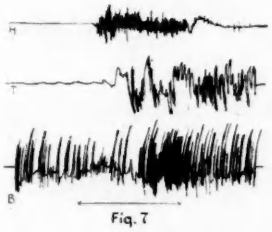

FIG. 7.—Monkey. Site 35; 7 v.

tory influence may be inadequate, and may result only in a temporary inhibition of the biceps at the onset of the triceps contraction as seen in fig. 7.

A modification of this response was observed some time later in the same animal. The spontaneous activity of the biceps had ceased and on a similar stimulation a hamstring-triceps response appeared at first which was unusual only that the triceps response was weak. Although the hamstring response continued during the period of stimulation, the triceps response was soon inhibited. A marked clonic response of the biceps appeared during this time which continued for a considerable period also in the form of an after-discharge.

It seems to follow from these experiments that the foci from which certain movements are elicited are more widely represented in the cortex than can be gathered from observations which were carried out on the

[1] This expression refers only to the assumption that a central structure is hyper-excitable but leaves the question of the site of this hyper-excitability undecided.

normal monkey, i.e. on animals lacking spontaneous activity in any one of their muscles. However, it has not been determined whether this phenomenon is due to cortical or subcortical facilitation.

It was observed previously (Murphy and Gellhorn, 1945, and other authors) that inhibition of tone or of spontaneous movements may follow stimulation of foci outside of the area from which ordinarily the muscles involved in these movements may be excited. Fig. 8a shows that stimulation of a focus in the lateral (prehension) area inhibits spontaneous tone of the hamstrings whose focus is located far more medially in the motor cortex. Apparently the tone of the hamstrings can be altered from a biceps-extensor carpi focus provided that the "hamstrings centre" is in a state of increased excitability, as suggested by spontaneous activity in

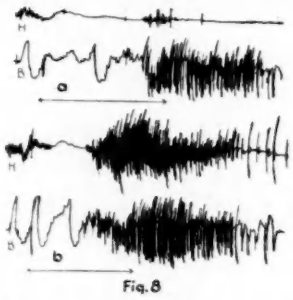

FIG. 8.—Monkey. Site 57; a = 6·3 v. and b = 7 v.

this muscle. A slightly stronger stimulus applied to the same site (fig. 8b) causes not only an inhibition but also, following this phase, a marked contraction of the hamstrings. This excitatory effect coincides with the contraction of the biceps.[1] Here again a motor effect results which is totally alien to the reactivity of a similar focus excited in a non-tonic monkey. The difference is twofold: First, a contraction of the hamstrings is elicited from the lateral sites of area 4; secondly, the contraction of the hamstrings is associated with that of the biceps instead of the triceps.

It was emphasized in the preceding investigation (Bosma and Gellhorn) that the hamstring muscles are activated as a part of the hamstring-triceps complex, which is elicited from the medial sections of area 4. If this is the case, it may be expected that tone in the hamstrings may alter the responsiveness of the cortex not only for these muscles but for the triceps as well. Fig. 9 seems to substantiate this inference. Fig. 9a shows

[1] A similar effect of a lesser degree may be seen at the end of the stimulatory period of fig. 8a.

on stimulation of a prehension site the peculiar hamstring-biceps response already described in a monkey with spontaneous activity in the hamstrings. There is practically no activity in the triceps at the same time. However, in the two subsequent experiments in which the responsiveness of the biceps had decreased, possibly owing to the marked activity including after-discharge of this muscle, a triceps-hamstring complex appeared. Following the activity of the triceps the biceps muscle contracts (fig. 9b).

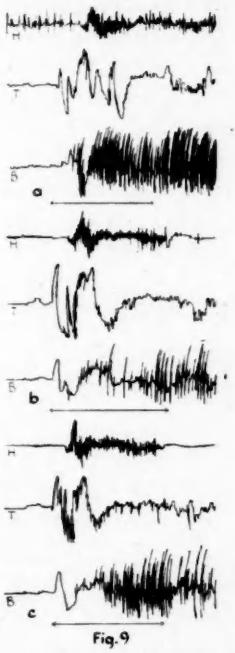

FIG. 9.—Monkey. Site 37; a = 4·8 v.; b = 8 v. and c = 10·8 v.

A similar result following the application of a slightly stronger stimulus is seen in fig. 9c. Although the triceps-hamstrings response clearly precedes that of the biceps the activity of the hamstrings continues throughout the period of stimulation. It is worthy of note that a reversal, i.e. triceps complex followed by biceps activity, is seen in these experiments as the result of a stimulation of a lateral part of area 4 although this effect is ordinarily obtained only from the intermediate zone of this area. Apparently, this extension of the zone of the reversal area is linked with the alteration of central excitability associated with spontaneous activity in the hamstring muscles.

Additional information was obtained in experiments on cats with spontaneous tone in one or more muscles. The experiment reproduced in fig. 10 is particularly instructive since degree and site of the tone varied considerably in this animal and permitted the study of the effect of tone on the cortically induced muscle response. Fig. 10a shows that the cortical stimulus causes a greater activity in the biceps than in the triceps muscle. This co-innervation accompanied slight flexion of the elbow. Some time later both muscles were in a state of tone and the same stimulation caused an increase in activity of the triceps and a decrease in the biceps muscle (fig. 10b). The final experiment (fig. 10c) shows spontaneous tone in the

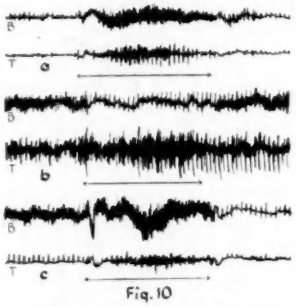

Fig. 10

FIG. 10.—Cat. Site: The middle of the cruciate sulcus. 3·3 v. The effect of cortical stimulation on biceps and triceps in different states of tonus.

biceps and no tone in the triceps muscle. The same cortical stimulus now again evokes a co-contraction of both muscles but the chief activity is seen in the biceps muscle. These observations indicate again that the type of muscular response is modified by the tone of the muscles which react to the cortical stimulus.

DISCUSSION.

The experiments reported in this paper are of interest from the point of view of normal as well as of pathological physiology of the motor cortex. The presence of tone in one or more muscles makes possible the study of the validity of the principle of reciprocal innervation. Examples of reciprocal innervation between antagonistic pairs such as biceps and triceps muscles and the hamstrings and the quadriceps have been described earlier by us. These experiments have been supplemented by the present work in which, in the monkey, the relation of the biceps group (biceps-extensor carpi) to the triceps complex (triceps-flexor carpi or, in the more medially located parts of area 4, triceps-hamstring muscles) was investigated. The

grouping of muscles into biceps or triceps complexes appears to be justified since under conditions of tonic activity the cortically induced inhibition of the tone in one muscle coincides with the appearance of activity in the whole or in parts of the antagonistic complex. Thus inhibition of the tone in the triceps muscle may be accompanied by the appearance of action potentials in either the biceps or the extensor carpi muscles or in both, depending on the locus and the intensity of cortical stimulation. Similarly, such inhibition may be associated with after-discharge of the antagonistic complex.

Whereas these data not only confirm but also extend the concept of reciprocal innervation and its validity for movements induced by cortical stimulation they are not in disagreement with our earlier observations on co-innervation. As a matter of fact, the finding that with increasing intensity of stimulation co-contraction of muscles of opposing functions appears in the cat (Bosma and Gellhorn, 1946) has been shown in the preceding paper to be valid for the monkey.

The investigation of motor effects induced by cortical stimulation in animals with tonic muscles is of considerable interest to the clinical investigator since it may throw some light on disturbances in innervation patterns observed in conditions in which alterations in tone occur as the result of extrapyramidal and upper motor neuron lesions as well as following excitatory processes involving the spinal reflex arc. It was shown in the present paper that the normal patterns of innervation (reciprocal innervation and co-innervation (co-contraction) may be absent in tonic muscles. Thus a tonic triceps may remain unaltered by a cortical stimulus which leads to a distinct contraction of the biceps muscle, whereas, in general, it would be inhibited by mild cortical stimuli and activated in the form of a co-contraction by somewhat stronger stimulation.

Of even greater interest is the fact that the motor effects resulting from stimulation of the cortex seem to be altered in animals with tonic muscles. It was shown in a preceding paper that the cortically induced response is characterized by definite electromyographic patterns which depend on the site of stimulation. This well-established cortical pattern is markedly altered since the tonically innervated muscle may be activated from areas which in the non-tonic animal call forth entirely different responses. Thus, the hamstring muscles commonly excited from the medial parts of area 4 with or without contraction of the triceps may be activated from the lateral aspects of this area. Since this area calls forth the biceps muscles a biceps-hamstring complex results. Whereas the various patterns of response described in the preceding paper appear to be purposeful and part of the progression reaction or of movements essential to grasping an

object with the hand, the elicitation of a simultaneous flexion of the knee and elbow on the same side seems definitely pathological since it would interfere with the maintenance of normal posture. The same abnormal pattern may, in a monkey with tonic biceps, result from stimulation of medial parts of area 4. These and other observations made on animals with tonic muscles show that contraction of the tonic muscle may be elicited from a wider cortical area than is found for the same muscle in a non-tonic animal. The pattern of movements is the result of a combination of the contraction of the tonic muscle with that of other muscles induced by a somewhat modified focal response of the motor cortex. Thus, the tonic biceps muscle, which responds with a contraction to a stimulation of a " triceps-hamstrings " focus, reacts in conjunction with the hamstrings, while the triceps response is held in abeyance. Reciprocal innervation appears even under these abnormal conditions.

These observations are closely related to earlier studies from this laboratory. L. Thompson and Gellhorn (1944) showed that stimuli leading to nociceptive afferent impulses modify cortically induced motor responses. On the basis of a comparison of reflex effects in spinal and in decerebrate animals, M. Thompson and Gellhorn (1945) pointed out the determining influence of muscle tone on quantitative and qualitative characteristics of spinal reflexes. Finally, experiments, as yet unpublished, indicate that the establishment of chronic contractures profoundly alter the effects of electrical stimulation of the motor cortex. These different groups of observations have the fact in common that afferent impulses originating in the muscles are involved. They seem to justify the statement that the effects of stimulation of the motor cortex are greatly modified by afferent nociceptive or propricoceptive impulses. These findings seem to be of importance for our understanding of the organization of the motor cortex. By the use of methods of stimulation involving cortical facilitation it was shown by Murphy and Gellhorn that from each cortical focus multiple muscles can be activated even after surgical isolation of that focus from the surrounding cortical areas. These data established experimentally, in contrast to the widely held mosaic hypothesis (cf. Murphy and Gellhorn for reference), the theory of multiple representation of cortical motor function recently advocated by Walshe (1942) on the basis of clinical and critical studies. The preceding paper by Bosma and Gellhorn confirmed these experiments and added new information showing the functional organization of the motor cortex within the frame of the multiplicity theory. The experiments described in this paper seem to indicate that the cortical map of the motor area depends to a large extent on afferent impulses. However, it cannot be decided without further experimentation to what degree this

effect is due to activation of neurons ordinarily not activated by cortical stimulation, to cortical spread of the excitatory process beyond the stimulated focus or to infracortical mechanisms.

Summary.

(1) Weak cortical stimuli applied to the motor cortex cause a temporary inhibition of a tonic muscle which may be followed by a distinct rebound occurring in the form of an after-discharge. Such after-discharge may also be observed in tonic muscles as the result of weak stimuli which, during the stimulation, fail to alter the activity of the tonic muscle.

(2) During the inhibition of the tonic triceps, activity in one or both constituents of the biceps complex (biceps and extensor carpi) may appear. If this activity continues in the form of an after-discharge the tone of the triceps may not reappear until the after-discharge has ceased. The principle of reciprocal innervation may, therefore, at least under favourable conditions, be valid for the after-discharge. However, the reciprocity rule shows numerous exceptions. To those previously studied may be added the fact that a biceps contraction may be induced by cortical stimulation while the tone of the triceps continues unchanged.

(3) Tonus in the triceps may prevent its contraction in the form of co-innervation (co-contraction) which is commonly seen to occur in conjunction with the moderate or strong contraction of the biceps elicited by cortical stimulation. However, co-contraction may be restored with disappearance of this tone.

(4) Tonic activity of the biceps may fundamentally alter the cortically induced motor response. Instead of obtaining from the medial zone of area 4 a hamstrings-triceps response, activity of the latter muscle may be abolished wholly or partially and in its stead a powerful contraction of the biceps may appear. Similarly it is shown that when the hamstrings are in tonic state, a stimulation of lateral sites in area 4 may cause a contraction of these muscles. Activity of the hamstrings is then associated with that of the biceps, in contradistinction to the hamstring-triceps pattern which appears in the non-tonic monkey on stimulation of the medial zone of area 4. The patho-physiological significance of this " substitution " is discussed.

REFERENCES.

Bosma, J. F., and Gellhorn, E. (1946), *J. Neurophysiology*, **9**, 263.

—— ——(1947), *Brain*, **70**, 127.

Murphy, J. P., and Gellhorn, E. (1945), *Archives of Neurology, Psychiatry*, **54**, 256.

Thompson, L., and Gellhorn, E. (1944), *Am. J. Physiol.*, **142**, 231.

Thompson, M., and Gellhorn, E. (1945), *Am. J. Physiol.*, **144**, 259.

Walshe, F. M. R. (1942), *Brain*, **66**, 104.

ATYPICAL INTRACEREBRAL HÆMORRHAGE

WITH SPECIAL REFERENCE TO CEREBRAL HÆMATOMA.

BY

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INTRACEREBRAL hæmorrhage, when it occurs in its usual form, presents a familiar clinico-pathological picture. The hypertensive, rather elderly man, while at work, suddenly develops headache which is often associated with vomiting. Consciousness is quickly lost and there are signs of hemiplegia. Blood may be found at lumbar puncture and death occurs in the course of a few hours or days. At autopsy arteriosclerosis is commonly found and the internal capsule and basal ganglia are the site of a hæmorrhage from rupture of a basal branch of the middle cerebral artery. As remarked by Boyd (1938), the small arteries to the basal ganglia come directly off the middle cerebral, so that the pressure is not "stepped down" by continuous branching as in the case of the cortical branches. The lenticulo-striate artery has for long been called "the artery of cerebral hæmorrhage" and probably three-quarters of the cases of intracerebral hæmorrhage conform to this rapidly fatal pattern.

Apart, however, from this well-recognized type of intracerebral bleeding, other less frequent and less fatal varieties occur and it is with these that this review is concerned. It is the purpose of the present paper

(1) to collect, both from the literature and from original records, certain examples of atypical intracerebral hæmorrhage,

(2) to discuss the various underlying ætiological factors in these cases,

(3) to give special consideration to the subcortical hæmatomata which are commonly the sequel to those hæmorrhages which are not quickly fatal, and

(4) to consider the possibilities of surgical treatment.

ILLUSTRATIVE CASE HISTORY.

The following case-history introduces a number of the problems in differential diagnosis, pathology and ætiology which have to be considered.

V. Y., a clergyman aged 56, was admitted to the National Hospital, under the care of Sir Charles Symonds, on October 24, 1946, complaining of weakness of the

right arm and right leg and difficulty in finding words. He had always been healthy but during the past month had seemed tired and forgetful. He gave no history of head injury but, on close questioning, he remembered having been dazed by a piece of wood which he was chopping some three or four months previously. He had suffered no impairment of consciousness, headache or other ill-effects, however, at that time. His wife recollected his remarking that he had stunned himself.

Two weeks before admission to hospital he complained of left-sided headache of gradual onset and he was slow in thought. The headache became more severe and five days before admission his right hand became weak, so that he was unable to hold a cup. He walked normally but on the following day his right leg was noticed to be weak. He was very drowsy and confused, saying little but "Yes" or "No." He became doubly incontinent and vomited once. During the two days before his admission there was considerable improvement in his speech and in the power of his limbs. On admission he was confused and retarded, showing blockage of thought and speech. He sighed frequently and had difficulty in conversing, although he was fully orientated and able to answer simple questions correctly. On attempting intelligence tests, such as the serial sevens, however, he began accurately but became progressively slower, more confused and inaccurate. There was bilateral impairment of sense of smell (more so on the left side than the right), and bilateral papilloedema. Hæmorrhage and exudate were seen around the right optic disc, which was more swollen than was the left. The pupils reacted sluggishly to light and accommodation but were otherwise normal and the visual fields were full to confrontation tests. There was a suggestion of right lower facial weakness, but the cranial nerves were otherwise normal. There were no motor or sensory changes in the upper limbs on admission and there was no grasp reflex. The tone of both lower limbs was increased, though power and sensation were normal. The abdominal reflexes were weaker on the right than on the left, and the knee-jerk and ankle-jerk were brisker on the right. The right plantar response, however, was repeatedly flexor and the left extensor. No abnormality of the cardiovascular or other system was discovered. His pulse rate was 62 and regular; his blood-pressure was 140/90. Plain X-ray of skull showed no abnormality.

Two days after admission his speech defect became more severe. He showed marked nominal aphasia with a tendency to jargon dysphasia, perseveration and clang association of words. He also became clumsy in the movements of his right hand.

It was considered that he probably had a left frontal tumour and ventriculography was carried out by Mr. Julian Taylor. The dura was under tension on both sides and the cerebrospinal fluid escaped in a jet. The fluid from the left lateral ventricle was straw-coloured from the beginning, and it became increasingly brown as the ventricle was drained. The X-ray views (reported on by Dr. J. W. D. Bull) showed the septum pellucidum to be displaced 0·5 cm. to the right and the left lateral ventricle to be slightly smaller than the right. Communicating with the left lateral ventricle was a cyst, roughly spherical in shape and about 4 cm. in diameter. The cyst lay in the frontal lobe, lateral to the anterior pole of the ventricle and reaching posteriorly as far as the plane of the Foramen of Monro. No nodular filling defect could be seen within the cyst

An operation was carried out by Mr. Julian Taylor on November 5, 1946. A left fronto-temporal osteoplastic flap was turned down, the dura punctured and a cannula inserted through the cortex. At a depth of about 1½ cm. it met with resistance which was overcome by a slight thrust. Fairly thick chocolate-coloured fluid then flowed through the cannula and some 15 to 20 c.c. were removed. The

dura was then more widely opened and the frontal cortex incised. This revealed at a depth of about 1½ cm. a well-defined dark capsule which, when in turn opened, released more of the chocolate-coloured fluid and some dark brown clots. A large vein connected with the Sylvian Vein appeared to drain part of the capsule and the medial side of the cavity had made connection with the frontal horn of the left lateral ventricle. The capsule and its contents were completely removed and the wound closed in stages without drainage.

Fluid from the cavity and the cyst itself were examined by Dr. J. G. Greenfield, who reported as follows:—

"The wall of the cyst consists of a fairly thin layer of dense collagen, shading off internally into fibroblastic granulation tissue and organization of the enclosed blood clot. External to the wall of collagen is a zone of fairly heavy admixture of plasma cells and many phagocytes containing blood pigment. The appearances indicate an old hæmorrhage which has become encapsulated by fibrous tissue. There is nothing in the structure of the wall to suggest that it is aneurysmal. A smear of the cyst fluid shows some leucocytes and many red cells. No organisms are seen and it is sterile to culture."

After operation the patient made good progress. His speech steadily improved and in about ten days he had no dysphasia, though he spoke in rather a measured style. He felt well, had no headache, was becoming increasingly alert mentally and had no trouble with his limbs. The papillœdema rapidly subsided and on December 6 Mr. Williamson Noble reported the appearance of his discs to be normal. Apart from some residual difficulty in close vision, he became entirely free from symptoms. He was able to play the organ for chapel services shortly before his discharge from hospital on December 12, 1946, and he has remained well since.

This rather striking case illustrates not only the value of full surgical investigation and treatment of such a condition, but it demonstrates how difficult may be the explanation of the origin of an intracerebral hæmatoma when one is found. The nature of the capsule indicates that this blood cyst was not of recent origin, although the sudden recent onset of symptoms suggests a recent fresh hæmorrhage. The clinico-pathological picture closely resembles the late variety of delayed traumatic apoplexy described by Symonds (1940) and to be referred to later, but what part, if any, was played by the minor blow on the head some three or four months previously can be a matter only for surmise. The distinction between so-called "spontaneous" and "traumatic" (particularly "delayed traumatic") intracerebral hæmorrhage becomes increasingly doubtful and difficult the more closely it is examined in cases of this description.

The Role of Arteriosclerosis and Hypertension.

Where cerebral hæmorrhage occurs in atypical form, vascular disease of this sort seems to be of relatively little significance. In a survey of over 40 cases of intracerebral hæmatoma, Buckley and McKinney (1941) described arteriosclerosis or hypertension in only 6.

Hawthorn (1922) reported two examples of fatal hæmorrhage in the earlier years of life. His two patients were youths of 17 years and 14 years respectively; each was in good health until the day of his death and in neither case was there any history of trauma. Post-mortem examination showed in the first case hæmorrhage deep in the substance of the mid-cerebellum, and in the second case hæmorrhage into the left frontal lobe and lateral ventricles. In neither instance was there any evidence of arterial disease. Hawthorne refers to a number of previously reported cases of cerebral and cerebellar hæmorrhages in early life. In some a mild head injury had preceded the apoplectic symptoms by days or weeks, but underlying disease was absent and the cause of the hæmorrhages remained unexplained.

Cerebral hæmorrhage occurring in young subjects in association with either essential hypertension or transient rise of blood-pressure is described by Kinnier Wilson (1940) and others.

In such circumstances one must imagine that a congenitally weak spot in a cerebral artery gives way as a sequel to altered vascular equilibrium induced by emotion or exertion.

In cases of persistent hypertension or arteriosclerosis in which superficial cerebral hæmorrhage occasionally develops, it has been supposed that rupture occurs at the site of a miliary aneurysm or other minute area of degenerated arterial wall. Charcot and Bouchard in 1868 first fully described these little saccules, about a millimetre or less in diameter, on the smaller arterial branches. Considerable doubt has since been expressed as to their significance. They do not always accompany atheroma, and other conjectural explanations of vascular rupture have been given.

A recent case in point, under the care of Dr. S. P. Meadows, was seen at the National Hospital.

Mrs. M. B., aged 47, was admitted to hospital in a very drowsy, confused state, complaining of severe headache. Eight days previously, when bending down, she suddenly developed a severe occipital headache, as if something had struck her. She fell down and was unconscious for a short time. She was put to bed at home, continued to have severe headache and vomited occasionally. On admission she had marked neck rigidity and positive Kernig's sign. There was no evidence of head injury. The margins of both optic discs were slightly blurred and the left pupil was slightly larger than the right. There was left facial weakness and marked weakness of the left upper and lower limbs. No obvious sensory loss could be detected. Tendon reflexes were absent apart from right triceps and right knee-jerk. The left plantar response was extensor and the right doubtful. Blood-pressure on admission was 220/110. In the first few days after admission she was doubly incontinent and the hemiparesis became more severe. Lumbar puncture on admission showed blood-stained fluid under pressure of over 300 mm. The Wassermann

reaction was negative. Lumbar puncture was repeated on two subsequent occasions within the next three days and the pressure and degree of blood-staining were each time diminished. She then made slow but steady improvement and after two months she was able to walk a few steps with assistance, although having a left spastic hemiparesis, with a grasp reflex and some impaired sensibility on the right side. She had a residual left homonymous hemianopia, had some difficulty in concentrating and was occasionally incontinent of urine at night. She was discharged from hospital after three months, still with left-sided spastic weakness, more marked in the upper than in the lower limb, and with a blood-pressure of 215/130.

It was considered that she had had an intracerebral hæmorrhage from part of the middle cerebral artery, with bleeding into the subarachnoid space. Whether in this instance it resulted from a miliary aneurysm or from a congenital aneurysm in the fissure of Sylvius can be only a matter for conjecture. The persistent hypertension and the onset of symptoms when stooping down suggest however that whatever the pathological basis the raised blood-pressure was the precipitating factor.

Post-mortem identification of miliary aneurysms causing intracerebral hæmorrhage is infrequent, as the aneurysmal sac is not only small but embedded in surrounding clot.

Green (1930), in an examination of the brains of arteriosclerotic subjects, recorded two miliary aneurysms arising from grossly diseased cerebral vessels, the subjects being men aged 57 and 59. These aneurysms were only about 0·5 mm. in diameter and were confined to the smaller arteries within the brain-substance. Green excludes from consideration the congenital berry-aneurysms which, though sometimes of minute size, are usually found on the larger arteries of the circle of Willis. He concludes that miliary aneurysms arise only when the media of an artery is involved to an extreme degree and that they may be responsible for cerebral hæmorrhage in some cases of arteriosclerosis.

It has thus become clear that although arteriosclerosis and hypertension may be contributory factors their presence is by no means essential for cerebral hæmorrhage since this may be encountered in a relatively young person who presents no evidence of generalized vascular disease and in whom the blood-pressure has been within normal limits.

Congenital Aneurysms.

Richardson and Hyland (1941) have drawn attention to the frequency of intracerebral hæmorrhage, often of large size, resulting from rupture of arteries in the subarachnoid space. In an analysis of autopsy findings in 27 cases of spontaneous subarachnoid hæmorrhage, they found that additional intracerebral bleeding had occurred in 19. The hæmorrhage in these cases was chiefly in the frontal and temporal lobes from aneurysms at the anterior part of the Circle of Willis. The bleeding into the brain may be much greater than the bleeding into the subarach-

noid space, and in three of their cases the latter was of only negligible amount. Although they encountered no purely intracerebral hæmorrhage from an aneurysm, they considered it to be likely that an aneurysm deeply embedded in the adjoining frontal or temporal lobe tissue might rupture directly into the brain substance without leaving a trace of subarachnoid hæmorrhage. They felt that "when a young or middle-aged person develops a sudden hemiplegia without obvious basis, such as hypertension, endocarditis or neurosyphilis, a ruptured berry aneurysm is the most likely explanation. If there is a bloody cerebrospinal fluid the diagnosis is much more certain, but it remains a definite possibility even without subarachnoid blood."

It is of interest that Gull in 1859, recording a case of a small aneurysm of the pons which ruptured, says: "Though intracranial aneurysms usually occur on the larger trunks of the vessels as they lie at the base of the brain or in the fissures between its lobes, the smaller branches, after entering the cerebral substance, are not exempt."

Collier (1931) recognized the occurrence of intracerebral hæmorrhage resulting from rupture either of a surface aneurysm adherent to the brain, or of an aneurysm buried in the brain-tissue.

Mallen (1933) described the case of a nine-year-old boy who, without previous illness or injury, suddenly became convulsed and comatose. Lumbar puncture showed clear colourless fluid under slightly increased pressure. At post-mortem examination there was no evidence of injury to the head but a recent blood clot, the size of a small walnut, was found in the right temporal lobe. The hæmorrhage was attributed to rupture of an aneurysm, though this could not be identified.

Hermann and Macgregor (1940) were probably the first to record a fatal case of verified congenital intracerebral aneurysm.

> The patient, a boy aged 4½ years, suddenly sat down, complained of left-sided headache, became convulsed and lost consciousness. Lumbar puncture showed blood-stained fluid under greatly increased pressure. Ventricular tap also showed blood on each side. He died fifteen hours after the onset of symptoms. At autopsy there was no abnormality of the brain surface but an extensive hæmorrhage had occurred into the left frontal lobe. An irregularly-shaped cavity, about 4 cm. in diameter, was filled with blood clot and had ruptured into the adjacent ventricle, the entire ventricular system being filled with blood clot. A ruptured aneurysm was found embedded in the wall of the hæmorrhagic cavity. The clot within the aneurysmal sac was continuous with the clot within the cavity. The aneurysm originated from a bifurcation of one of the deep branches of the anterior cerebral artery within the brain substance. Just posterior to the aneurysm a second smaller aneurysm was found. It had not ruptured but lay exposed upon the wall of the hæmorrhagic cavity.

Hamby (1945) refers to the autopsy findings in a 50-year-old man who

had an extensive hæmorrhage into the left temporal lobe, extending into the lateral ventricle. There was a pea-sized aneurysm, with an opening on its cerebral surface, on the middle cerebral artery, partly fixed in position by an older organized clot.

Congenital aneurysms are a common cause of cerebral hæmorrhage in young people. In such cases the seat of the aneurysm is likely to be the middle cerebral artery in the fissure of Sylvius. In many instances a diagnosis of rupture of such an aneurysm rests on presumptive evidence, based on the clinical history. When the aneurysm is deeply embedded the hæmorrhage may be ingravescent in character, with rather gradual onset of symptoms.

Other Vascular Anomalies.

Congenital vascular abnormalities other than aneurysm may in some cases underlie a sudden intracerebral hæmorrhage. Elkington (1935) describes the case of a woman of 27, in whom post-mortem examination showed that hæmorrhage had occurred from a pre-existing telangiectasis of the left half of the pons and left middle cerebellar peduncle. This was not associated with any vascular abnormality elsewhere. He discusses cases from the literature showing that it is not only capillary telangiectases which are liable to give rise to intracerebral hæmorrhage in apparently healthy people, but that similar vascular accidents may occur in association with malformations composed of larger vessels—i.e. arteriovenous angiomata. The telangiectases are commonly symptomless unless hæmorrhage or thrombosis takes place, and a number of cases of sudden death from hæmorrhage into these structures is on record.

Though they have been described in all parts of the brain, the capillary telangiectases are commonest in the contents of the posterior fossa. The arteriovenous anomalies, on the other hand, appear to have a preference for the posterior part of the cerebral hemispheres.

According to Dandy (1928), cerebral hæmorrhage occurs in about 40 per cent. of cases of arteriovenous angioma. He regards this condition as one of the commonest causes of cerebral hæmorrhage during youth or middle age. Gordon Holmes (1931) reports the case of a woman of 30 who for six months before her death suffered from occipital headaches and then suddenly developed a left homonymous hemianopia. Autopsy showed that the right occipital lobe was the site of an arteriovenous angioma which had given rise to a hæmorrhage, destroying the depths of the calcarine fissue. Levine (1933) records two fatal cases of intraventricular hæmorrhage from arteriovenous angioma in the temporal and parietal lobes.

Turner (1937) also reports a fatal case of intracerebral and intraventricular hæmorrhage from an arteriovenous angioma. The angioma was seen as a wedge-shaped mass of tangled thick-walled vessels in the lower part of the right temporal and occipital lobes and extending into the lateral ventricle. In the right parietal lobe was a large subcortical cystic cavity which contained blood and apparently represented recent hæmorrhage into an area of encephalomalacia.

Penfield (1936) refers to a fatal case of intracerebral hæmorrhage in a man aged 30 with an old history of fractured occipital bone in childhood. At operation there was "what looked like a hæmangioma, or at least a carpet of blood-vessels on the brain just beneath the old fracture," from which it was thought the hæmorrhage must have come.

Hawkins and Rewell (1946) report two cases of unheralded fatal hæmorrhage in subjects aged 18 years and 19 years. At autopsy massive hæmorrhage was found in cerebellum and cerebrum respectively and no source of bleeding was obvious to the naked eye. Microscopic sections of the edge of the area of hæmorrhage in each case, however, showed a tangle of thin-walled blood-vessels, regarded as cavernous hæmangiomata. It is possible, therefore, that some of the unexplained cases of intracerebral hæmorrhage may result from small angiomatous formations which are invisible to the naked eye and which should be searched for by careful section and microscopy of the edge of an area of hæmorrhage.

Kidd and Cumings (1947) suggest that there is a familial tendency in the formation of some angiomata. They discuss an Icelandic family and give clinical and post-mortem records of two of its members.

> The one, a woman aged 33, developed hemiparesis, dysphasia, and died in coma four days later. At autopsy an angiomatous condition was found in the left cerebral hemisphere, into which hæmorrhage had taken place. The other case was that of her cousin, a man aged 22, who was admitted in coma with spasticity of the limbs, more pronounced on the left side. He developed right-sided papillœdema, was found to have blood-stained cerebrospinal fluid, and died after twelve days. He had also had an attack of unconsciousness eight months previously. At autopsy there was a cyst containing yellow fluid in the left temporal lobe and a large recent hæmorrhage in the right temporoparietal lobe. The hæmorrhage was so extensive that it was impossible to demonstrate any angioma.

The striking feature is that no less than eight other members of two generations of this family died suddenly in youth, apparently from similar cerebrovascular accidents.

Vascular anomalies of such a sort may therefore be considered with berry aneurysms as a congenital and possibly familial factor underlying certain cases of intracerebral hæmorrhage, especially in young people.

Eclampsia.

De Lee (1938) states that cerebral hæmorrhage of varying degree is found in 40 per cent. of cases of eclampsia at autopsy. The type of hæmorrhage varies from small petechiæ to a massive hæmorrhage into the frontal or occipital lobe or internal capsule.

Abbott (1941) reports a case of eclampsia, in which an intracerebral hæmorrhage into the occipital area led to stupor, bilateral papillœdema and left homonymous hemianopia. Ventriculography showed clear fluid under pressure with displacement of the ventricular system to the left and defective filling of the posterior horn of the right lateral ventricle. A trocar, inserted into the right occipital lobe, showed clots of old blood and, on incision of the cortex, a blood clot weighing 8 grammes was removed. The patient made a satisfactory recovery apart from a residual homonymous hemianopia. The presence of syphilis and arteriosclerosis were eliminated and the condition was believed to have been precipitated by the combination of a toxic state and sudden rise in blood-pressure.

Cerebral Tumour.

In the differential diagnosis of intracerebral hæmatoma from neoplasm the combination of the two conditions has to be considered, since hæmorrhage may of course occur into a pre-existing cerebral tumour. This, however, is an uncommon complication.

Oldberg (1933) analysed the histories of 832 consecutive cases of glioma, verified by operation or autopsy and found that gross hæmorrhage had occurred in only 3·7 per cent. Hæmorrhage accompanied by appropriate clinical symptoms had occurred in only 7 or 0·84 per cent. of the 832 cases.

Vascular Occlusion.

Syphilitic arterial disease is more often associated with cerebral thrombosis than with hæmorrhage. The condition is primarily a generalized endarteritis and therefore localized weakening and aneurysmal formation in the cerebral vessels are not ordinarily found. In a minority of cases, however, where there is vascular occlusion or thrombosis, the syphilitic infection may indirectly result in the production of a patch of cerebral softening into which hæmorrhage may subsequently occur.

Cerebral hæmorrhage of varying degree and of venous origin may occur with thrombosis of the superior longitudinal sinus and involvement of the middle cerebral veins.

Vascular occlusion from an embolus produces analogous effects. In the case of infective endocarditis, an infected embolus is particularly likely

to occlude and damage the coats of a cerebral vessel, leading to the formation of a mycotic aneurysm which subsequently ruptures. The symptoms in such cases may be either sudden or gradual in onset.

Polyarteritis Nodosa.

Polyarteritis nodosa is a rare but important condition leading to aneurysm formation, thrombosis and hæmorrhage, in which the brain may sometimes be involved. Such a case was recently seen at the National Hospital.

M. W., a male aged 51, was admitted under the care of Dr. F. M. R. Walshe in June 1945, complaining of intermittent pains in the extremities, beginning about a year previously. He had experienced burning pains, vasomotor changes and blistering of the finger-tips. His arms and legs had become thin and he noticed weakness of his wrists and ankles with dragging of the right foot. He had lost weight generally and had recently had a bout of fever. On examination, the only abnormal neurological findings were wasting and weakness of the limbs with right foot-drop, diminished arm-jerks, absent ankle-jerks and loss of position sense in the toes. Dr. Walshe diagnosed peripheral neuritis, probably due to polyarteritis nodosa. One week after admission the patient suddenly had symptoms of a cerebral hæmorrhage, from which he died the same day. A post-mortem examination was made by Dr. J. G. Greenfield, part of whose report was as follows:—

"There was a rather large left parieto-occipital hæmorrhage coming near the surface and bursting out of it both over the outer surface of the occipital pole and in the parietal region about one inch to the left of the midline. The arteries at the base appeared quite free from atheroma or disease. On section of the brain several hæmorrhages into the ventral parts of the pons and mid-brain were found. The heart appeared normal and the kidneys showed little fibrosis or evidence of scarring. Histologically, some of the larger arteries in the kidney show early lesions of polyarteritis nodosa, i.e. hyaline degeneration of the whole thickness of the wall, which is invaded by histiocytes, and invasion of the surrounding fibrous tissue with plasma cells and lymphocytes."

Histological changes typical of polyarteritis nodosa could not be identified elsewhere, but the clinical diagnosis was regarded as confirmed.

Arkin (1930) gives the incidence of involvement of the central nervous system (apart from peripheral nerves) in polyarteritis nodosa as 8 per cent. He describes two such cases. In the one, autopsy showed multiple foci of hæmorrhage of various sizes up to 2 cm. in the cerebellar cortex. In the other, there was a large fresh cerebral hæmorrhage in the region of the left basal ganglia and reaching almost to the cortex, with perforation into the left lateral ventricle.

Trauma—Immediate Effects.

Intracerebral hæmorrhage with hæmatoma formation may result immediately from head injury. A recent case admitted under the care of Mr. Harvey Jackson was as follows:

A man, F. B., aged 39, was knocked down by a motor van and died eight days later, having remained unconscious since the accident. He had scalp wounds in the right parietal and occipital regions, and a left flaccid hemiplegia. X-ray showed no fracture of the skull. The cerebrospinal fluid (CSF), on lumbar puncture, was blood-stained. Post-mortem examination showed petechial hæmorrhages throughout both cerebral hemispheres and a large hæmorrhage in the substance of the right cerebral hemisphere running about half an inch above the lateral ventricle. There was only a small amount of blood on the surface of the brain.

Sometimes lumbar puncture in cases of this type reveals clear colourless cerebrospinal fluid, and the differential diagnosis between localized intracerebral hæmorrhage and thrombosis may be difficult.

For example, Mrs. J. O., aged 19, was admitted under the care of Mr. Harvey Jackson to a Head Injuries Hospital, having been injured in an accident with a motor tractor two days previously. She was conscious but drowsy, and had a period of post-traumatic amnesia of about twenty-four hours. She did not complain of headache and had not vomited. She had some facial lacerations and a fractured left angle of the mandible, but there were no scalp wounds and X-ray showed no skull fracture. She had a flaccid left hemiplegia, with some attention defect in the left homonymous visual field. There was gross impairment of deep and superficial sensibility over the whole of the left side of the body. Tendon reflexes were brisker on the left than on the right, the left abdominal responses were absent, those on the right being normal, while the left plantar response was extensor and the right flexor. Lumbar puncture on the day after admission showed clear colourless cerebrospinal fluid, no cells being seen. Her mental state gradually improved and after about two weeks there was some return of power, first in the upper limb and then in the lower limb. Sensibility to pin-prick and light touch returned to normal with the improvement in her mental condition, but stereognosis and complete loss of two-point discrimination on the left side of the body persisted. Postural sense and vibration sense seemed unimpaired. Some ten weeks after the accident she was able to walk with support, but the left leg was still very weak and the left hand useless. She was discharged from hospital and continued to make slight progress. When seen seven months later she had marked spastic hemiparesis but was able to walk without support. The cortical sensory loss was unchanged. It was considered that this was a case of either cerebral thrombosis or intracerebral hæmorrhage of traumatic origin.

The extent of the motor and sensory loss, the absence of headache and vomiting and the presence of a clear cerebrospinal fluid are in favour of a diagnosis of thrombosis, but a clear cerebrospinal fluid cannot be held to exclude the diagnosis of cerebral hæmorrhage. Merritt (1938) points out that cerebral hæmorrhages rupture into the ventriculosubarachnoid space in only 75 per cent. of the fatal cases, and probably in a much smaller percentage of the non-fatal cases. It is possible, therefore, that some post-traumatic cases of this type may result not from cerebral thrombosis but from intracerebral hæmorrhage.

Courville and Blomquist (1940) have discussed the effect of trauma in producing cerebral hæmorrhage otherwise than by direct laceration of the brain. They describe two varieties of traumatic intracerebral hæmorrhage

resulting from coup-contrecoup mechanism. According to them, the injury is sustained with the head in motion and the intracerebral hæmorrhage tends to be produced either directly beneath the point of injury or on the opposite side. The first variety is "adjacent" or "secondary" hæmorrhage, which is provoked usually by contusion of the temporal and frontal lobes; the second is "central" or "primary" and occurs usually in the centrum of the frontal or temporal lobes, without evidence of regional contusion or laceration of the overlying surface of the brain. Such hæmorrhages, particularly those occurring inside the temporal lobe, may become manifest clinically after a variable interval of lucidity. They may pursue a progressive course in a patient who has never been rendered entirely unconscious. If extensive, they may eventually rupture into the ventricles and may lead to a mistaken diagnosis of subdural hæmatoma. Courville and Blomquist state that the internal capsule is less apt to be injured by blunt trauma than any other part of the brain, and in a series of 38 cases of post-traumatic intracerebral hæmorrhage they found no example of gross hæmorrhage into the posterior limb of the internal capsule, such as appears spontaneously in cases of hypertension or arteriosclerosis. Kaufmann (1929) had previously emphasized the point that it is rare to find a traumatic hæmorrhage in the basal ganglia, where the usual arteriosclerotic hæmorrhages are so frequent.

Intracerebral hæmorrhage after trauma is found to occur in young as well as in older people, and arteriosclerosis itself seems to play no important part in the production of such hæmorrhages, though, according to Courville and Blomquist, it may have a mild predisposing influence.

Holden and Le Marquand (1929) gave a clinical description of what appeared to be a case of intracerebral hæmorrhage in a healthy girl of 9 years who, after a trivial knock on the forehead, developed headache, spasmodic jerking of the left leg, deviation of head and eyes to the right, vomiting and loss of consciousness. About ten minutes elapsed between the accident and complete coma. The trauma was so slight that it left no mark on the head. After six hours she regained consciousness and had a complete left flaccid hemiplegia. There were no other symptoms, her blood-pressure was within normal limits, and thereafter she made steady improvement.

A typical case of acute post-traumatic bleeding in the depth or centrum of the temporal lobe is described by Pilcher (1941).

A boy, aged 5 years, fell 5 feet, striking the back of his head on a concrete floor twenty hours before admission. He did not lose consciousness but developed drowsiness, headache and vomiting. X-ray of skull showed no fracture. Next day he

developed a right hemiplegia with aphasia, stiffness of neck and early papillœdema. The cerebrospinal fluid was tinged with blood. A burr hole was made in the left temporal region. There was no extradural or subdural hæmorrhage but about 3 cm. below the cortex a cavity containing liquid blood clot was encountered and drained by a blunt needle. The hemiplegia disappeared rapidly, speech returned on the fifth post-operative day and he was discharged on the seventh day, free from symptoms.

A somewhat similar case is described by Naffziger and Jones (1928), although they regard the hæmorrhage as a delayed effect.

The patient was a man aged 42 who was hit on the right temple, and was unconscious for a brief period. X-ray examination showed a linear fracture of the right temporal bone but no depressed fracture. In the next thirty-six hours he had increasing headache, with gradually increasing stupor and bradycardia. With this there appeared an incomplete left hemiplegia. A diagnosis of middle meningeal hæmorrhage was made and a decompression operation was performed. An extremely tense but otherwise apparently normal dura was exposed, without evidence of extradural bleeding. The dura was opened and revealed temporal lobe, normal in appearance apart from a very small area where the cortex showed bluish discoloration. Puncture of the temporal lobe through the discoloured area was made and at a depth of 2 or 3 cm. a large hæmorrhage was encountered and some 3 ounces of black coagulated blood were removed. After this the tension was reduced to normal and no fresh bleeding occurred. The patient made an uneventful recovery and four years later was well, apart from a slight spasticity of the lower limb and moderately impaired use of the upper limb.

Whether trauma is the sole cause or merely the precipitating factor in such cases is difficult of proof. It is noteworthy, however, that in the post-traumatic cases the hæmorrhage is more liable to form a circumscribed clot or hæmatoma than in the cases of hæmorrhage associated with evident vascular abnormality. Consequently the clinical picture produced by the former is more likely to be that of a space-occupying and often expanding intracerebral lesion, while in the latter it is more likely to be apoplectic.

Trauma—Delayed Effects.

In some instances the trauma seems relatively trivial and there is a considerable interval of time between the head injury and the onset of symptoms. This is the condition of delayed traumatic intracerebral hæmorrhage, or " traumatische Spätapoplexie " as originally described by Bollinger in 1891.

Bollinger's five patients died suddenly of apoplectiform hæmorrhage after a period of lucidity varying from twelve to fifty days after injury to the head. In only one of them was there in fact gross hæmorrhage into the cerebrum. The remaining four showed hæmorrhage chiefly into the fourth ventricle. In spite of considerable controversy the conception of delayed traumatic apoplexy as an entity, independent of pre-existing

vascular disease, has survived. Neither fracture of the skull nor loss of consciousness need occur, and the interval between the injury and development of symptoms is usually regarded as varying between one day and eight weeks (Naffziger and Jones, 1928; De Jong, 1942).

Symonds (1940) recognises a late variety of delayed traumatic apoplexy in which the interval between injury and apoplexy may be several months or years. In this variety he suggests that the symptoms result from fresh hæmorrhage into the cystic cavity of a chronic cerebral hæmatoma.

Since Bollinger's account, occasional cases of delayed traumatic apoplexy have been reported and these have been referred to by De Jong (1942), who reported two further fatal cases. Naffziger and Jones (1928) give an account of three cases with operative recovery. The hæmorrhage in each of their cases was in the right cerebral hemisphere.

Their third case, which is perhaps the only one to fall strictly into the "Spätapoplexie" group, was that of a man aged 30 who received a slight blow to his head in a motor accident. There was no impairment of consciousness, no sign of injury, and X-ray of skull showed no fracture. Next day he complained of slight headache but he continued at business as usual. Five days after the injury, on getting up in the morning, he was suddenly seized with generalized headache, vertigo and vomiting. He was put to bed in a drowsy, restless state, complaining of severe headache. His left pupil was larger than his right and there was a left hemiparesis, with left homonymous hemianopia. In the course of the next two weeks he developed marked bilateral papillœdema with hæmorrhages. He also showed a paresis of the left 6th nerve and sensory impairment over the left side of the body as well as a flaccid hemiplegia with increased tendon reflexes on the left. By the eighteenth day after injury the patient was deeply stuporose, with feeble respiration and slow irregular pulse. Considering the possibility of a chronic subdural hæmatoma, a large right temporoparietal bone flap was turned. The dura was extremely tense but there was no sign of extra- or subdural bleeding. A small opening was made in the dura in the region of the supramarginal gyrus and a ventricular needle was passed into the brain substance. At a depth of about 3 cm. a large hæmorrhage was encountered and thick tarry blood escaped through the needle. The cavity was irrigated and the wound closed. He very rapidly became less stuporose and by the time he had returned to his room he was able to perform gross movements with both left limbs. At the time of the patient's discharge from hospital, four months after the operation, the strength of the limbs was equal, the hemianopia was less evident and continued to improve.

A case recorded by Rosenhagen (1930) is referred to by Symonds (1940) as one of the most convincing examples of delayed traumatic intracerebral hæmorrhage.

The patient, a healthy man of 27, fell from a train and sustained slight injuries to his head and face. He did not lose consciousness but was confused and subsequently had headache. Five weeks after the accident he returned to work against medical advice. Three weeks later he woke in the night with severe headache and found his left limbs weak. He was admitted to hospital, comatose with a left hemiplegia. The cerebrospinal fluid contained no blood. He died eight hours later. At post-mortem a recent hæmorrhage the size of an apple was found in the white

matter of the right fronto-parietal region. No aneurysm or other source of the hæmorrhage could be found.

Doughty (1938) reports 4 cases of mild head injury without loss of consciousness in young males who, after an interval of time (varying from a few days to four months). suddenly developed symptoms and signs suggestive of intracerebral hæmorrhage, and this condition was in each case confirmed.

One patient was a man of 24 who received a kick on the right parietal area. About four months later he complained of headache, nausea and vomiting. Two weeks later he bumped his forehead: in a few minutes he developed severe headache and nausea and lost consciousness. His cerebrospinal fluid was blood-stained. A decompression operation was undertaken but he died on the table. At post-mortem a massive hæmorrhage was found in the left cerebrum lateral to the ventricle and completely collapsing it.

This case probably falls into the group described by Symonds as the late variety of delayed traumatic apoplexy, in which fresh hæmorrhage is believed to occur into a cyst resulting from intracerebral hæmorrhage at the time of injury. In the case reported by Symonds there was a history of three successive head injuries, each suggestive of some intracerebral hæmorrhage, at the ages of 10, 19 and 26 years respectively. It was presumed that the second injury caused further hæmorrhage into a small cyst remaining from the first injury. The third injury caused further and more extensive leakage and the symptoms of an expanding intracerebral lesion appeared. At operation a quantity of brownish yellow fluid was withdrawn from an intracerebral cyst, part of the wall of which was examined histologically and showed no evidence of new growth. The patient made an uninterrupted recovery.

Other instances of post-traumatic cerebral hæmorrhage with delayed symptoms simulating those of brain tumour have been recorded from time to time. Ecker and Love (1939) describe the case of

An 11-year old boy who suffered a mild head injury, without bone injury or loss of consciousness; he had no symptoms, except intermittent headaches, for four years before evidence of increasing intracranial pressure appeared. He then had three generalized convulsions with loss of consciousness and some subsequent focal symptoms and bilateral papilloedema. A burr hole was made in the left frontal region and a cannula introduced. About 3 cm. below the surface a hæmorrhagic cyst was encountered and 30 c.c. of old thick blood was recovered. Biopsy showed no tumour, convalescence was uneventful and the symptoms and signs cleared up.

Ernstene (1937) describes a case of

A man of 48 who fell from a scaffold and was momentarily unconscious but had no sign of injury to his head. Six months later he began to complain of some occipital headache but felt well in general until twelve months after his fall, when

severe headache suddenly developed. He became confused and had a generalized convulsion, with loss of consciousness for ten to fifteen minutes. After this he remained confused and dysphasic. He had bilateral papillœdema and a right superior quadrantic field defect. Lumbar puncture showed clear colourless cerebrospinal fluid under pressure of 340 mm. A diagnosis of left temporal tumour was made and craniotomy performed. When the temporal lobe was incised a large cavity was found containing an old dark semi-fluid blood clot. No tumour tissue was found in the wall of the cavity but the presence of some dilated veins suggested that the intracerebral hæmorrhage might have been associated with a vascular anomaly.

Craig and Adson (1936) describe two cases in which hæmorrhage apparently resulted from trauma.

The first was that of a youth of 18 who was admitted on account of generalized convulsions. Nineteen months previously he had been struck on the right occiput by a golf ball which knocked him down. He was not concussed and was able to walk home, but his vision was slightly blurred and he developed headache and vomiting. The vomiting continued for about a week and the blurred vision for twelve days; the headache persisted intermittently. Seven months after the accident he began to have generalized convulsions with periods of loss of consciousness lasting about ten minutes. At the time of the first convulsion he fell and injured his head. Neurological examination was negative apart from a left homonymous hemianopia for colours. A bone flap was turned over the right temporo-occipital region and resistance was encountered about 2½ cm. below the surface of the brain. The wall of a cyst was punctured and soft blood clot, believed to be of venous origin, was aspirated. The patient became free from symptoms apart from the field defect for colours.

Their second case was that of

A man aged 39 who was admitted on account of headache in the left occipital region and weakness of the right side of the face and body of three months' duration. He had fallen six months previously and had struck his head in the left occipito-parietal region. He was dazed for five minutes and felt weak for four days. His hemiparesis developed fairly suddenly three months later, after an attack of "weakness all over" and a roaring noise in his head. Weakness and numbness of the right side varied from day to day. He developed aphasia and was found to have bilateral papillœdema. Craniotomy over the left parietal lobe was performed and, on incision of the cortex, tarry blood exuded. The cyst was irrigated and a laminated clot was removed. The patient did well and hemiplegia and hemianæsthesia cleared up.

This last case in many ways resembles that of Mr. V. Y., described earlier in this paper, and both may represent the type of delayed post-traumatic intracerebral hæmorrhage envisaged by Symonds.

Unexplained Hæmorrhage.

The distinction between post-traumatic and so-called spontaneous intracerebral hæmatoma is difficult to draw, especially in the cases where there is a history of a mild head injury some weeks or months before the onset of severe symptoms.

Connor (1939) described a case in which intracerebral hæmorrhage of doubtful origin occurred. The fact that the patient,

A boy of 17, had had "a possible mild head injury while wrestling" the day before the onset of symptoms serves to show how difficult it may be to assess the significance of mild head injury in precipitating the symptoms. The boy suddenly developed headache, dizziness, vomiting and fell to the ground with a left hemiplegia. He became stuporose and showed blurring of the optic discs. Craniotomy was performed, the posterior part of the right frontal lobe was incised and at a depth of 2½ cm. there was a gush of 5 c.c. of blood and a cavity approximately 3 cm. in diameter was exposed. No tumour cells were found in its wall. The patient was subsequently discharged, with diminishing symptoms.

In one of Craig and Adson's further cases the hæmorrhage was believed to be traumatic in origin, even though the head injury occurred twelve years previously. In five of the remaining six cases no adequate explanation for the hæmorrhage could be found and it is noteworthy that in six of their total of nine cases the age of the patients was under 40.

Lack of recognition of the occurrence of non-traumatic intracerebral hæmorrhage even in young subjects has led to a number of cases being reported as delayed traumatic apoplexy when the previous trauma was of doubtful significance. Even in the presence of advanced arteriosclerosis, severe injury to the head has been found to result usually in marked contusion of the brain rather than in localized intracerebral hæmorrhage.

One of Craig and Adson's patients, in whom no cause for hæmorrhage could be found, was

A woman aged 30, admitted to hospital complaining of paralysis and numbness of the right side. She had been perfectly well until five weeks before admission, when she awoke with numbness of the right hand and some dysphasia. This persisted and the right leg then felt numb. By the third day she was unable to walk and the following day she had a complete right hemiplegia with right facial weakness. Headache developed three weeks after the numbness. Previous history was negative. X-ray of skull was normal. Her blood-pressure was 100/65 mm.Hg and the visual fields and fundi were normal. She was believed to have a rapidly growing cerebral tumour and the left temporoparietal region was explored. A subcortical hæmatoma was encountered about 3 cm. below the surface and a black tarry mass was removed, leaving a cavity about 3 cm. in diameter. The vessels in the surrounding brain tissue were normal. After operation the patient recovered completely from her aphasia and sensory impairment and almost completely from the hemiplegia.

Hæmatomata resulting from intracerebral hæmorrhage of obscure ætiology have also been described by Bagley (1932), Klemme (1941), Pilcher (1941) and Buckley and McKinney (1941).

Klemme describes 6 cases of non-traumatic intracerebral hæmatoma, in none of which was there evidence of vascular disease or other predisposing factors. Their average age was 34 years and the predominant

clinical findings were headache, dimness of vision or other visual symptoms, associated with hemiplegia and papillœdema. The clot was localized by ventriculography in 5 of these cases and in all 6 cases large subcortical clots were successfully removed at operation.

Pilcher describes 8 cases of subcortical hæmatoma treated surgically. 3, or possibly 4, of these were post-traumatic, but 4 were "spontaneous" in that no causative factors could be found. Except for the ætiological factor, there were no essential differences between the cases of traumatic and spontaneous hæmorrhage. In 6 of the 8 cases the patients were under middle age and 3 of them were under 20. The onset of symptoms was sudden. Convulsions occurred in 5 cases and in 3 of these the seizures were focal. Stupor, coma, vomiting, aphasia and hemiplegia also developed in certain cases. In one case in which ataxia and cranial nerve palsies developed, the hæmatoma was found in the left cerebellar hemisphere.

No ætiological factor was found to account for 10 out of 41 cases of intracerebral hæmatomata, surgically treated, collected by Buckley and McKinney. In half the cases reviewed by them there was a history of head injury though not necessarily either severe or recent.

The origin of this group of intracerebral hæmatomata therefore remains obscure.

Location of Hæmorrhage.

The location of intracerebral hæmatomata of the type described has been found to be relatively superficial and there is little to distinguish those resulting from trauma from those of more obscure ætiology. They have been found in the frontal, temporal, parietal and occipital lobes, generally a few centimetres below the surface.

Buckley and McKinney (1941) and Hamby (1945) have summarized the location of intracerebral hæmatomata, as recorded by various workers. The fronto-parietal and temporal regions appear to be the commonest sites.

Spontaneous hæmorrhage into the cerebellum is rare, but Pilcher (1941), in recording one such case, refers to others in which it has been reported.

Development of the Hæmatoma.

The nature and fate of the blood shed beneath the surface of the brain seems to be somewhat variable. Immediately after the intracerebral hæmorrhage has occurred, the fresh semi-solid clot is surrounded only by the compressed cerebral tissue. The brain is tense and there is marked

venous distension. Penfield (1936) has called attention to the characteristic discoloration of cortex overlying a subcortical hæmatoma. Browder and Turney (1942) found clotted blood in the brains of patients dying a few hours after injury. Twelve to fifteen hours later the clot was "syrupy." Hamby (1945) states, however, that he is unable to reach any conclusion as to the type of clot to be found at any particular stage of the lesions, that when such a clot is aspirated, old fluid blood can be obtained from almost all of them and when the cyst is opened, practically all of them contain solid clot, at any time after hæmorrhage. It seems that the blood partly coagulates and then undergoes gradual liquefaction.

Bagley (1932) states that when there is an immediate outpouring of blood with little or no subsequent oozing, the formation of a cyst through liquefaction of the clot and organization of the surrounding tissues begins within the first few days.

The adjacent cerebral substance forms a capsule by proliferation of the glia and connective tissue around the hæmorrhagic focus. The coagulum tends to become gradually absorbed and, as described by Buzzard and Greenfield (1921), the final results may be either a large single cavity containing more or less blood-stained fluid, a multilocular cavity or a linear scar. Fluid-filled cysts may persist for years after the hæmorrhage. If repeated hæmorrhages occur, laminated clots may be found.

Craig and Adson (1936), Symonds (1940) and Rowbotham and Ogilvie (1945) have referred to the type of chronic intracerebral hæmatoma in which signs of increased intracranial pressure develop and the symptoms resemble those of an intracranial neoplasm. According to Rowbotham and Ogilvie, as the clot breaks down, its molecular content increases, leading to a rise in osmotic pressure, so that fluid is drawn into the blood clot from surrounding tissues to form a blood cyst of increasing size. A cyst wall also forms and the process may be somewhat analogous to the development of a chronic subdural hæmatoma.

Calcification may ultimately develop either in the capsular wall (Pilcher, 1941) or in the hæmatoma itself. Levin (1927) reported the removal from the left temporoparietal region of the brain of a hard mass, which, when sectioned, proved to be both laminated and calcified. It contained traces of altered blood pigment and had the features of a calcified hæmatoma. Grantham and Smolik (1942) describe the removal of a calcified spherical mass, 30 grammes in weight, from the right occipital lobe of a patient who was believed to have had a hæmorrhage at this site thirty-three years previously following a head injury.

The Nature of "Spontaneous" Hæmorrhage.

Gross intracerebral hæmorrhage of the subcortical variety has thus been seen to occur in association with intracranial aneurysms and other vascular abnormalities and also at variable intervals of time after head injury. In some cases the vascular and traumatic factors may operate together. In other cases, of which examples have already been given, no obvious causes can be found and many of these so-called "spontaneous" or unexplained hæmorrhages occur in young people.

Attempts to account for this last variety have been based on the idea of pathological changes in the blood-vessels.

The early conception was of simple fatty degeneration of the small arteries and their capillaries. Degenerative changes in the blood-vessels were then considered to result in the formation of miliary aneurysms which ruptured without leaving any trace of aneurysmal dilatation.

The importance of intracerebral aneurysms in the production of obscure cerebral hæmorrhage came to be doubted by later workers and more attention was paid to the relationship of the vessel walls and the surrounding brain tissue.

Globus and Strauss (1927), in discussing the general problem of cerebral hæmorrhage, returned to Rouchoux's conception of a "pre-hæmorrhagic" stage of softening, preceding apoplexy. Rouchoux as early as 1814 maintained that a weakened vessel wall and a sudden rise in tension were insufficient to produce hæmorrhage unless there were a previously diminished resistance in the brain tissue near a degenerating blood-vessel. Globus and Strauss presented clinical and pathological evidence to suggest that cerebral hæmorrhage is but a terminal event in a chain of circumstances and that disease of the cerebral vessels results in the first instance in closure of one or more of such vessels in a circumscribed area. This leads to the creation of an ischæmic zone and a consequent focal encephalomalacia. With the production of such cerebral softening, an area of diminished resistance develops and the way is thus prepared for hæmorrhage to occur.

The primary cause, by this theory, is believed to be disease of the vessels and no satisfactory answer is therefore provided as to the cause of cerebral hæmorrhage in a young person without evidence of generalized or localized vascular disease and in whom the blood-pressure has been within normal limits.

Westphal and Baer (1926) suggested that in some cases the hæmorrhage was preceded by a period of angiospasm. They believed that during the stage of vascular spasm the immediately surrounding tissue was damaged

or altered so that, after the return of blood into the vessels, this tissue did not offer sufficient resistance to the vessel wall and leakage occurred.

It is postulated that spasm may occur in normal cerebral arteries and that this may lead to intracerebral hæmorrhage in individuals without evidence of cardiovascular disease. Craig and Adson (1936), however, in considering the ætiology of spontaneous cerebral hæmorrhage were impressed by the fact that after removal of clot and exploration of the cavity at operation, there were no active bleeding points and that the condition appeared to have resulted from slow oozing rather than from sudden extensive extravasation. They believed therefore that the hæmorrhage was of venous rather than arterial origin.

Although explanations in terms of local vascular spasm or degeneration may account for some of the otherwise obscure cases of spontaneous intracerebral hæmorrhage in young subjects, it is evident that in many instances no adequate reason can be found.

The Nature of Delayed Post-Traumatic Hæmorrhage.

The pathogenesis of delayed traumatic apoplexy has caused considerable controversy but three main conceptions have been expressed.

The first is Bollinger's own view that necrotic softening of cerebral tissue results from even mild head injury and that this subsequently leads to hæmorrhage, due in part to alteration of the walls of an artery and in part to weakening of the tissue resistance around the vessel.

The second point of view supposes that abnormalities of the vessel walls precede the trauma. Langerhans (1903) was an early exponent of this view and he and subsequent writers have expressed the opinion that vascular disease, particularly arteriosclerosis or aneurysm, is present in all such cases and that trauma should be considered only a precipitating factor.

The third conception of post-traumatic hæmorrhage applies particularly to those cases in which the onset of symptoms is considerably delayed. Von Hölder (1904) from his microscopic studies first described the formation of initial tears of small vessels, aneurysmal dilatations and focal hæmorrhages which may result directly from injury and which he believed paved the way for a later and larger hæmorrhage in the vicinity. The view that delayed hæmorrhage may develop in a focus of primary hæmorrhage which occurred at the time of the injury has been accepted by other and later workers. Browder and Turney (1942) refer to repeated small hæmorrhages, the total volume of which eventually produces focal signs; they state that they have observed relatively large intracerebral

hæmatomas with a laminated appearance strongly suggesting repeated episodes of bleeding. Craig and Adson (1936) also referred to two cases in which lamination of clot occurred and a fresh clot had formed in the dependent portion of the original clot as if recurrent hæmorrhages had taken place.

Symonds (1940) divides cases of delayed traumatic apoplexy into an early and a late group. He considers that the former (in which symptoms occur within a few weeks of injury) result from traumatic weakening of an arterial wall while the latter (in which the interval between injury and apoplexy may be several months or years) result from secondary hæmorrhage into an original blood cyst caused at the time of the injury.

To revert to the first conception of Bollinger, it is of interest that more recent work has elaborated his ideas. Thus Helford (1939) believes that angionecrosis may result from damage to surrounding brain tissue but that tissue destruction itself may sometimes result from vasomotor paralysis consequent upon contrecoup impetus of the cortex against the bony vault. De Jong (1942) also accepts the idea of a "pathophysiologic" mechanism resulting from trauma and consisting of vascular spasm leading to local necrosis; he describes a case in which hæmorrhage occurred into such a necrotic area. He believes that this type of angiospasm may occur in either normal or pathological vessels but probably takes place with less stimulation or trauma in the latter.

De Jong found no sign of atherosclerosis in the cases of post-traumatic intracerebral hæmorrhage described by him and it is now clear that the second viewpoint referred to above provides an inadequate explanation. It fails to account for the delay in onset of symptoms, unless it be by the formation of a gradually increasing hæmatoma. It also fails to account for those cases of post-traumatic cerebral hæmorrhage where there is no evidence of vascular disease.

Courville and Blomquist (1940) draw the following conclusions from their histological investigations:—

"Arteriosclerosis in itself does not seem to play an important part in the production of these hæmorrhages, although it may have a mild predisposing influence. There seems to be no greater incidence of gross intracerebral hæmorrhage in persons with advanced arteriosclerosis and associated severe injuries than in younger adults. Other rarer conditions, such as hypoplasia of the arteries or other vascular disease, may play a minor role in the production of post-traumatic hæmorrhages."

The presence of vascular abnormalities is not essential, but if they happen to occur, they may predispose to post-traumatic hæmorrhage.

Ernstene (1937) has described a case of intracerebral hæmorrhage, with symptoms commencing some months after trauma, in which at operation a large cavity, containing dark semi-fluid blood clot, was found in the left temporal lobe. A large blood-vessel, apparently a thrombosed vein, pursued a vertical course through the anterior portion of the cavity and two other greatly dilated veins were seen in the neighbourhood. The Sylvian vein on the other hand was unusually small. In view of these findings and the absence of tumour tissue in the wall of the hæmatoma, it was concluded that the underlying cause of the hæmorrhage was a vascular anomaly.

The Role of Thrombosis.

It seems possible that delayed post-traumatic intracerebral hæmorrhage may in some cases result from encephalomalacia of the type that Bollinger envisaged but consequent upon thrombosis.

De Veer and Browder (1942) have described a fatal case of infarction of the brain, induced by thrombosis of the middle cerebral artery in a man of 42.

The patient had sustained a severe head injury with unconsciousness for twenty minutes, followed by a period of relative lucidity for about twelve hours, after which he gradually became stuporose and hemiplegic. He died fifty-seven hours after the injury. The gross anatomical findings were thrombosis of the right internal carotid artery and its middle cerebral branch with encephalomalacia of the right basal ganglionic area and absence of hæmorrhage. Microscopic examination of the middle cerebral artery revealed a laceration of the intima and media without perforation or hæmorrhage. This was considered to be the result of the recent severe head injury. Traumatic cerebral thrombosis in a less vital region might well lead to softening of brain tissue around a vessel with subsequent hæmorrhage.

The development of temporary focal symptoms such as hemiplegia and aphasia several days after a head injury is sometimes seen and this may be explained in terms of either a small hæmorrhage or thrombosis. In the absence of blood in the CSF a clinical distinction may be impossible, but the occurrence of such cases suggests that small areas of encephalomalacia may develop in such a way without symptoms until at a later date bleeding occurs into them, producing the picture of delayed traumatic cerebral hæmorrhage.

The following cases, for whose records I am indebted to Mr. Harvey Jackson, illustrate the delayed development of focal signs after head injury

and the difficulty of making a pathological diagnosis of hæmorrhage or thrombosis from the clinical picture.

E. R., a man aged 54, was cranking his car when another car ran into the back of it and he was knocked down. He was concussed, with a post-traumatic amnesia of some hours. He was taken to hospital semiconscious, with a cut on the back of his head, a fractured right clavicle and multiple bruises. X-ray of skull showed a fissure fracture in the right posterior parietal area. There were no abnormal neurological findings and he made good progress until nineteen days later when he became drowsy and had an epileptiform attack involving the left side of the body. After the fit he regained full consciousness and showed no confusion or dysphasia. He had minimal residual weakness of the left upper and lower limbs but there was left homonymous hemianopia and gross cortical sensory impairment on the left side of the body. The tendon reflexes showed no obvious abnormality, though the left plantar response was only doubtfully flexor. The optic discs were normal and the blood-pressure was 105/70 mm.Hg. He continued to have intermittent epileptic attacks for several days, the clonic movements being generalized but more marked on the left side. Lumbar puncture two days after the first epileptic attack showed very faintly yellow fluid containing 26 cells per c.mm. (the majority being polymorphonuclear cells). He made rapid progress and in two weeks' time the hemianopia had practically disappeared and there was no motor or sensory impairment. He was discharged a month later.

Mrs. A. L., aged 63, received a minor head injury as a result of a flying bomb explosion on July 20, 1944. She was cut behind the left ear and over the left eyebrow, but was able to return home the same day after out-patient treatment. She continued to attend daily till July 29, when the wounds had healed, X-ray of skull showed no abnormality and she was discharged well. Some 4½ weeks after her injury there was a fairly rapid onset of right hemiplegia with headache and dysphasia. She was readmitted to hospital on September 4, 1944, when she was found to be alert but to have gross receptive and executive dysphasia with dyspraxia. She had a right homonymous hemianopia, normal pupils, slight blurring of the nasal margin of the left optic disc, right facial weakness and right hemiplegia of spastic type with right extensor plantar response. Sensation could not be accurately tested but was considered to be defective on the right side. Her blood-pressure was 230/150 mm.Hg. Lumbar puncture on September 28 showed clear colourless fluid under pressure of 180 mm., containing 4 lymphocytes per c.mm. and 80 mgm. protein per 100 c.c. The electroencephalogram showed a high voltage disturbance at a rate of 1½ to 2 per second on the left side, maximal in the frontotemporal region. The tracing suggested an extensive cortical or subcortical lesion and it was considered extremely unlikely that such a record could be produced by extracerebral bleeding. The patient made very satisfactory progress in hospital. The optic discs were reported as normal on September 11 and a month later her dysphasia had much improved. She was discharged on October 31 with only very slight speech defect and minimal right-sided weakness. When seen again a month later, she was feeling well and showed still further improvement.

Mrs. H. S., aged 60, was admitted to hospital as an air-raid casualty on February 10, 1943. She was unconscious, had a scalp wound in the left parietal area and was bleeding from both ears. Tendon reflexes were absent. She had five convulsions and vomited shortly after admission. Her cerebrospinal fluid on lumbar puncture was heavily blood-stained. Next day her general condition was improved and she was able to respond to simple instructions. There was no obvious motor or sensory impairment. Optic discs appeared normal. Tendon reflexes were present, the

right knee-jerk being brisker than the left and the right plantar response equivocal while the left was flexor. Within the next three or four days she gradually recovered full consciousness and answered questions normally. Vision appeared normal, but the left pupil was slightly smaller than the right. X-rays of skull showed no abnormality. She continued to improve until about February 23 when over the course of twenty-four to forty-eight hours she developed a complete right-sided hemiplegia and severe aphasia. Optic discs remained normal, right plantar response was extensor and left flexor. Lumbar puncture on February 23 showed pale yellow cerebrospinal fluid under pressure of 45 mm. and containing 1 lymphocyte per c.mm. During the following four weeks she made remarkably good progress and fully regained her speech. She was discharged on April 29 with only slight right-sided weakness. The tendon reflexes on the right side were brisker than on the left, but both plantar responses were flexor. She was seen again a year later and was found to be feeling well though she had occasional paræsthesiæ in the right hand. The physical findings were unchanged.

The following case illustrates the sudden development of intracerebral hæmorrhage in an area of brain which was softened and œdematous as the result of a penetrating injury nine days previously.

Capt. A. H., a man aged 29, was admitted to a Head Injuries Hospital on July 25, 1942, with a compound depressed fracture in the left parietal region. He had been attending a demonstration of explosives the same evening. He was about 400 yards from the explosion and was not wearing a steel helmet. After hearing the explosion he was aware of a queer numb feeling in the mouth and an ache in the left side of the head. He did not lose consciousness. He realized that he had been hit and was taken first to the nearest hospital where his scalp wound was probed and a superficial foreign body removed. The wound was filled with sulphanilamide powder and he was then transferred to the Head Injuries Hospital. He was then drowsy and vomiting but able to answer questions coherently. There were no abnormal neurological findings. X-ray of skull showed a depressed fracture 1 inch in diameter in the left parietal bone. He was operated on again within eight hours of the injury by Mr. E. B. C. Hughes. The scalp wound was excised and enlarged. A saucer-shaped depressed fracture of the skull with some loose bone fragments was seen at the base of the wound. A burr hole was made to one side and loose fragments were removed. The dura showed a small tear about one-third inch long. The underlying cortex appeared to be normal. The dura and scalp were sutured in layers, with a small corrugated drain, which was removed next day. Although rather drowsy, he remained well after operation and full clinical examination of his nervous system revealed no abnormality.

Early on August 3 (nine days after injury) he suddenly became noisy and was found to have a severe right hemiplegia, affecting the face and upper limb rather more than the lower limb. He was conscious but dysphasic. The wound was at once re-explored by Mr. Hughes. There was no sign of infection, no extradural hæmorrhage and the dura itself appeared to be quite healthy. On opening the dura the surface of the cortex was discoloured purplish-red over an area of about one square inch. This was incised and a fairly large intracerebral clot was found, lying just under the surface of the cortex and extending inwards for about two inches. This clot was removed by gentle suction and irrigation. The walls of the cavity consisted of grey œdematous brain which was gently removed by irrigation and suction until normal cerebral tissue was observed in all parts of the cavity. The wound was then closed in layers with drainage. After operation there was

gradual but steady improvement in the power of the right side and his comprehension of written and spoken speech also showed marked improvement. There was some cortical type of sensory loss in the right hand. The optic discs were normal and he became free from drowsiness or headache. He was discharged from hospital on October 3, 1942, with some residual spastic weakness of the right hand and executive dysphasia.

Cases such as these last four suggest that cerebral softening which may result either directly from trauma or indirectly from cerebral thrombosis, produced by trauma, may be the antecedent of delayed traumatic intracerebral hæmorrhage. It seems reasonable to suppose that preliminary thrombosis, bruising and softening may present no localizing signs and that it is only when hæmorrhage and hæmatoma formation occur that marked symptoms are likely to become manifest. Cerebral bruising after head injury occurs most frequently in the cortex of the frontal, temporal and occipital poles and it is just below the surface in these regions that delayed cerebral hæmorrhage is most likely to occur.

Many of the signs may result from pressure on surrounding cerebral tissue produced by a gradually expanding hæmatoma. Surgical evacuation of the hæmatoma frequently results in the disappearance of such signs. The first case described in this paper is an example of such an instance, and mention has been made of others.

Surgical Treatment.

The surgical treatment of intracerebral hæmorrhage was first described by Cushing (1903). He reported the case of

A negro aged 40, who, after a fall from a bicycle, became unconscious and developed a right hemiplegia with conjugate deviation of eyes to the right. Two days later a left osteoplastic bone flap was turned and a probe was passed into the substance of the brain. "When the probe had entered a distance of 4 cm. a sudden lack of resistance was encountered as though it had entered a cavity, and dark blackish fluid blood spurted out along the groove of the instrument." The handle of a scalpel was then introduced and "about two teaspoonfuls of old, discoloured, semi-fluid blood and clots" were evacuated. Next day the patient's condition had greatly improved, but he died on the third day from pulmonary complications.

Cushing commented: "The propriety of surgical procedures of this sort doubtless will be questioned by many, and I believe that only in exceptional cases will surgical measures hold out any prospect of success. . . . I do not see any reason why we should exclude these cases from possibilities of surgical relief simply because the hæmorrhage lies beneath the cortex, any more than that intracranial hæmorrhage in other situations should be allowed to run its course."

Russell and Sargent (1909) were also amongst the first to carry out surgical treatment in cases of this type. They record the case of

A woman of 54 who had an apoplectic attack, and when seen ten days later was unconscious and had a complete right hemiplegia. On the eleventh day a bone flap was turned down over the left parietal region and a trocar inserted into the post-central gyrus. Along this a few drops of dark, thick treacly blood exuded. An incision was then made through the cortex and more blood of the same nature escaped. A finger was then inserted and a cavity about the size of a walnut was found. From this some 3 drachms of altered blood was allowed to escape. The patient made a satisfactory recovery from the operation. She remained aphasic and hemiparetic but otherwise well.

Russell and Sargent considered the operation to be justified in a few selected cases of apoplectic hæmorrhage, particularly those with strictly unilateral symptoms indicative of a localized hæmorrhage in the white matter, not flooding the ventricles, with deep coma and high blood-pressure.

Penfield (1933) reported two cases in which surgical intervention was successfully carried out. The first,

A boy of 14, had aphasia with right hemiplegia and at operation a large clot of blood was removed from his left temporal lobe. No cause for the hæmorrhage was found and he recovered, except for some weakness of the right hand. The second case was a hypertensive woman aged 40 who over a period of six days gradually developed dizziness, drowsiness and headache, with nausea, vomiting, right hemi-anæsthesia, right hemipåresis, aphasia, and right homonymous hemianopia. She became convulsed, was found to have early papillœdema with xanthochromic cerebrospinal fluid under pressure of 290 mm. water. Ventriculography on the eighteenth day showed displacement to the right, and at operation the following day a large clot was removed from the left occipital lobe. The patient recovered rapidly except for hemianopia, but she died suddenly six months later.

Penfield pointed out that the blood clot in such cases is almost always large and that the more favourable and operable cases do not die early, so that opportunity for surgical intervention presents itself over a period of days or even weeks. He concluded that for the time being the place for surgery in the treatment of intracerebral hæmorrhage must be a very small one but with careful study and selection of cases it might be possible to do something, if only temporarily, for a larger number.

In the past fifteen years there have been several further reports of successful removal of intracerebral hæmatomata, both of the so-called "spontaneous" and traumatic varieties.

Craig and Adson (1936) described the successful evacuation of clots in 9 cases of intracerebral hæmorrhage, marked symptomatic improvement resulting in almost all. Hamby (1945) reported 16 cases of gross intracerebral hæmatomata treated by surgical drainage with 14 recoveries and 2 deaths. He believes that surgery should be considered in cases with apoplectic or gradual onset, with progression of signs and the development of evidence of increased intracranial pressure. Encephalography or ventriculography should be used if localization is not evident.

Successful operative treatment has also been reported by Naffziger and Jones (1928), Bagley (1932), de Lauwereyns (1934), Ernstene (1937), Doughty (1938), Ecker and Love (1939), Connor (1939), Symonds (1940), Pilcher (1941), Abbott (1941), Furlow, Carr and Wattenberg (1941), Klemme (1941), Buckley and McKinney (1941) and Rowbotham and Ogilvie (1945).

The operative procedure consists of removal of a small piece of bone or turning of an osteoplastic flap, opening the dura and localization of the hæmatoma by a brain cannula. The brain tissue is then usually incised and liquid or solid clot removed by gentle suction. The dura may be left open to provide a decompression. In very early stages aspiration may be adequate while well-encapsulated lesions require radical extirpation.

In a number of the cases surgically treated the pre-operative diagnosis was cerebral tumour. There is little doubt that the most favourable cases for operation are those in which the development of the syndrome of increased intracranial pressure is gradual and accompanied by signs of a lesion implicating the more accessible areas of the brain.

SUMMARY.

Although cerebral hæmorrhage commonly takes the form of massive intracapsular bleeding in an arteriosclerotic subject, less frequently hæmorrhage may develop elsewhere in the brain, usually fairly close beneath the cerebral cortex in a young and apparently healthy individual.

In the latter group, generalized arteriosclerosis appears to play little or no part, but small intracerebral aneurysms, angiomata or other vascular anomalies have sometimes been identified as the source of the hæmorrhage. Special conditions such as eclampsia, cerebral tumour, polyarteritis nodosa and mycotic aneurysm account for a few of the cases.

Head injury, even when apparently slight, is an important ætiological factor, and may produce immediate or delayed effects.

In other instances a history of head injury is either absent or so remote that doubt must be cast on its significance. There thus remains a number of cases where the hæmorrhage is "spontaneous" in that no adequate explanation can be given. Clinically and pathologically, however, these cases are as a rule indistinguishable from the delayed post-traumatic variety.

In the majority of these cases the clinical picture is not one of sudden apoplexy but rather of a slowly expanding intracerebral lesion. This

results from the development of a subcortical hæmatoma which tends to become encysted and to increase in size.

Clinical examples of subcortical hæmorrhage are described and the location, nature and development of the resultant hæmatoma are discussed.

Some of the cases of non-traumatic hæmorrhage may be accounted for, if not by a simple inherent tendency to bleed, by vascular spasm with the subsequent production of small areas of cerebral softening, into which hæmorrhage readily occurs. Microscopic angiomata may account for others.

Differing views as to the nature of delayed post-traumatic hæmorrhage have been expressed. Pre-existing vascular disease is not necessarily present. The head injury may cause angiospasm, leading to ischæmic necrosis and cerebral softening, or, alternatively, the cerebral softening may result directly from the injury. In either event a focus of encephalomalacia is produced into which bleeding from an altered vessel readily occurs. This bleeding may be a sudden, gradual or repeated process.

It may be difficult to distinguish between cerebral hæmorrhage and cerebral thrombosis after trauma. It is suggested that traumatic cerebral thrombosis may in some cases be the precursor of delayed post-traumatic cerebral hæmorrhage.

Delayed post-traumatic cerebral hæmorrhage and other types of subcortical hæmatoma of obscure origin may mimic subdural hæmatoma or cerebral neoplasm.

The results of full investigation and surgical treatment of this type of cerebral hæmorrhage have been encouraging, particularly when the signs have been those of gradually increasing intracranial pressure.

I wish to express my thanks to members of the staff of the National Hospital for permission to quote cases admitted under their care. I am also especially grateful to Sir Charles Symonds and to Dr. J. G. Greenfield for their encouragement and helpful criticism in the preparation of this paper.

REFERENCES.

ABBOTT, W. D. (1941), *J. Amer. Med. Ass.*, **117** (ii), 1439.
ARKIN, A. (1930), *Amer. J. Path.*, **6**, 401.
BAGLEY, C. (1932), *Arch. Neurol. Psychiat.*, **27**, 1133.
BOLLINGER, O. (1891), "Uber traumatische Spätapoplexie." Internat. Beiträge zur wiss. Med. Festschrift Rud. Virchow. Berlin.
BOYD, W. (1938), "Textbook of Pathology," London, 3rd Edn., p. 888.
BROWDER, J., and TURNEY, M. F. (1942), *N.Y. St. J. Med.*, **42**, 2230.
BUCKLEY, P. J., and MCKINNEY, J. M. (1941), *New Engl. J. Med.*, **224**, 716.
BUZZARD, E. F., and GREENFIELD, J. G. (1921), "Pathology of the Nervous System," London.

CHARCOT, J. M., and BOUCHARD, M. C. (1868), *Arch. Physiol, Paris*, **1**, 110.
COLLIER, J. (1931), *Brit. Med. J.*, **2**, 519.
CONNOR, G. J. (1939), *Yale J. Biol. Med.*, **12**, 97.
COURVILLE, C. B., and BLOMQUIST, O. A. (1940), *Arch. Surg. Chicago*, **41**, 1.
CRAIG, W. McK., and ADSON, A. W. (1936), *Arch. Neurol. Psychiat.*, **35**, 701.
CUSHING, H. (1903), *Amer. J. Med. Sci.*, **125**, 1017.
DANDY, W. E. (1928), *Arch. Surg. Chicago*, **17**, 190.
DE JONG, R. N. (1942), *Arch. Neurol. Psychiat.*, **48**, 257.
DE LAUWEREYNS, J. (1934), *Bull. Soc. Nat. Chir.*, **60**, 228.
DE LEE, J. B. (1938), "Principles and Practice of Obstetrics," Philadelphia.
DE VEER, J. A., and BROWDER, J. (1942), *J. Neuropath. Exper. Neurol.*, **1**, 24.
DOUGHTY, R. G. (1938), *Southern Med. J.*, **31**, 254.
ECKER, A. D., and LOVE, J. G. (1939), *Proc. Mayo Clin.*, **14**, 107.
ELKINGTON, J. ST. C. (1935), *Lancet*, **1**, 6.
ERNSTENE, A. C. (1937), *Surg. Clin. N. Amer.*, **17**, 1431.
FURLOW, L. T., CARR, A. D., and WATTENBERG, C. (1941), *Surgery*, **9**, 758.
GLOBUS, J., and STRAUSS, I. (1927), *Arch. Neurol. Psychiat.*, **18**, 215.
GRANTHAM, E. G., and SMOLIK, E. A. (1942), *Ann. Surg.*, **115**, 465.
GREEN, F. H. K. (1930), *J. Path. Bact.*, **33**, 71.
GULL, W. (1859), *Guy's Hosp. Rep.*, **5**, 281.
HAMBY, W. B. (1945), *N.Y. St. J. Med.*, **45**, 866.
HAWKINS, C. F., and REWELL, R. E. (1946), *Guy's Hosp. Rep.*, **95**, 88.
HAWTHORNE, C. O. (1922), *Practitioner*, **109**, 425.
HELFORD, M. (1939), *J. Nerv. Ment. Dis.*, **90**, 157.
HERMANN, K., and MACGREGOR, A. R. (1940), *Brit. Med. J.*, **1**, 523.
HOLDEN, G. H. R., and LE MARQUAND, H. S. (1929), *Lancet*, **1**, 229.
HOLMES, G. M. (1931), Brain, **54**, 470.
KAUFMANN, E. (1929), "Pathology for Students and Practitioners," Philadelphia, Vol. 3, p. 1890.
KIDD, H. A., and CUMINGS, J. N. (1947), *Lancet*, **1**, 747.
KLEMME, R. M. (1941), *Surgery*, **10**, 434.
LANGERHANS, R. (1903), "Die traumatische Spätapoplexie," Berlin.
LEVIN, J. J. (1927) *Brit. J. Surg.*, **14**, 215.
LEVINE, V. (1933), *Arch. Path.*, **15**, 340.
MALLEN, L. R. (1933). *Med. J. Aust.*, **1**, 496.
MERRITT, H. H. (1938), *Med. Clin. N. Amer.*, **22**, 577.
NAFFZIGER, H. C., and JONES, O. W. (1928), *California and West Med.*, **29**, 361.
OLDBERG, E. (1933), *Arch. Neurol. Psychiat.*, **30**, 1061.
PENFIELD, W. (1933), *Canad. Med. Ass. J.*, **28**, 369.
—— (1936) (Discussion) *Arch. Neurol. Psychiat.*, **35**, 716.
PILCHER, C. (1941), *Arch. Neurol. Psychiat.*, **46**, 416.
RICHARDSON, J. C., and HYLAND, H. H. (1941), *Medicine*, **20**, 1.
ROSENHAGEN, H. (1930), *Dtsch. Z. Nervenheilk.*, **114**, 29.
ROWBOTHAM, G. F., and OGILVIE, A. G. (1945), *Brit. Med. J.*, **1**, 146.
RUSSELL, A. E., and SARGENT, P. (1909), *Proc. R. Soc. Med.*, **2**, 44.
SYMONDS, C. P. (1940), *Brit. Med. J.*, **1**, 1048.
TURNER, O. A. (1937), *Arch. Path.*, **24**, 223.
VON HOLDER, H. (1904), "Pathologische Anatomie der Gehirnerschütterung beim Menschen," Stuttgart.
WESTPHAL, K., and BAER, R. (1926), *Dtsch. Arch. Klin. Med.*, **151**, 1.
WILSON, S. A. K. (1940), "Neurology," London, p. 1069.

THE TERMINAL CONNEXIONS OF THE OLFACTORY TRACT IN THE RABBIT.

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It is commonly stated in textbooks of human anatomy that the fibres of the olfactory tract terminate in three main regions: (1) the parolfactory area (including the sub-callosal gyrus) and the septal area, (2) the grey matter of the anterior perforated substance (which includes the indistinctly developed " olfactory tubercle ") and (3) the cortex of the uncus and hippocampal gyrus, and possibly some of the nuclear elements of the amygdaloid complex. An attempt to discover the factual evidence for such statements leads to disappointing results, for they appear to be based either on the study of fibre preparations of normal material or on the use of the Marchi method for demonstrating degenerating fibres in experimental material. Both these methods are inconclusive and, indeed, often misleading. The information which they provide is necessarily of a provisional nature and always needs to be tested by more refined technical methods. The same criticism can be applied to statements concerning the connexions of other parts of the olfactory system of the brain which are commonly accepted as established facts. There is need, therefore, to undertake a complete revision of this system, and the present communication represents part of a research programme which is being undertaken in this department to that end. Before giving an account of our experimental study on the terminal connexions of the olfactory tract, it is desirable to clarify certain general points regarding the structure of those parts of the brain which are currently believed to be olfactory "centres." We shall not, however, attempt to give a complete review of all those olfactory connexions which have from time to time been described on the basis of normal material. In some recent descriptive articles on the fibre connexions of the non-cortical centres of the telencephalon there are extensive references to work on this subject (e.g. Humphrey, 1936, and Young, 1936), and attention is

particularly drawn to a recent critical review by Brodal (1947) on the supposed relationship of the hippocampus to the sense of smell.

In lower mammals, the lateral olfactory tract can be traced without difficulty on to the surface of the so-called piriform lobe. It is often assumed, therefore, that the cortex of the piriform lobe is entirely olfactory in function. But it needs to be recognized that the cortex is not homogeneous in structure and connexions. It includes, for example, the area piriformis (peri-amygdaloid and prepiriform areas of cortex), a cortical element of the amygdaloid complex, and the area entorhinalis. In the rabbit (according to Brodmann's charts) the entorhinal area forms a considerable proportion of the whole piriform lobe. It corresponds to the area piriformis posterior described by Gray (1924) in the opossum, which this author homologizes with Cajal's "écorce temporale postérieure ou supérieure" in the cat and the rabbit. Cajal states that this area of the cortex receives no terminal fibres of the lateral olfactory tract, and Gray is in agreement with this conclusion. It appears from these (and other) observations that, in the first place, only a limited part of the cortex of the piriform lobe receives direct connexions from the olfactory bulb. This limited part includes the prepiriform area, that is, the area of the piriform cortex which receives the terminals of the lateral olfactory tract (or the area piriformis anterior of Gray) and which extends forwards to become continuous eventually with the grey matter of the olfactory bulb, and also the peri-amygdaloid cortex.

The amygdaloid "nucleus" is really a complex of several nuclei which were defined over twenty years ago by Johnston (1923). His nomenclature has been generally followed by subsequent workers and we shall adopt it here. Johnston recognized six amygdaloid nuclei which he divided into two main groups on structural and comparative anatomical grounds. The more primitive and phylogenetically ancient group is closely related in connexions and grade of development to the basal olfactory areas, and comprises the central, medial and cortical nuclei, and the nucleus of the lateral olfactory tract. The more recently developed components of the amygdaloid complex are represented by the basal and lateral nuclei which appear to be formed by an infolding and migration of cells from the region of the entorhinal sulcus. The central amygdaloid nucleus, it should be noted, forms a matrix through which the fasciculi of the stria terminalis spread out to reach other amygdaloid nuclei, and it is in fact directly continuous with the bed nucleus of the stria. This bed becomes stretched in the higher vertebrates to form a very attenuated band of grey matter which extends from the amygdaloid region (near the tip of the temporal

pole of the cerebral hemisphere) to the base of the olfactory peduncle, and through the latter it is eventually continuous with the central grey matter of the olfactory bulb. Serial sections also demonstrate the continuity of the bed nucleus of the stria terminalis with the bed nucleus of the anterior commissure and with the anterior olfactory nucleus. Thus there are very clear topographical reasons for supposing that the stria terminalis and its bed nucleus are an integral part of the olfactory system of the brain. According to the Marchi studies of Fox (1943), lesions of the stria terminalis between the thalamus and the tail of the caudate nucleus always result in a forward degeneration, and it is thus assumed that the fibres of the stria are efferent with respect to the amygdala; on the other hand, no retrograde cell degeneration was observed after section of the stria. The precise relation of the stria to the various amygdaloid nuclei has still to be determined, though the Marchi experiments to which reference has just been made suggest that, while many of the fibres arise in the basal nucleus, none take origin from the lateral nucleus. The connexions of the olfactory tract fibres with the amygdaloid nuclei are also uncertain, since statements concerning them rest almost entirely on the doubtful evidence of normal fibre preparations. Cajal could not establish such a terminal connexion, but, as the result of descriptive studies made since his time, it seems to be generally accepted that fascicles of the lateral olfactory tract end in those amygdaloid nuclei which lie close to the surface of the piriform lobe. On the other hand, no fibres showing Marchi degeneration have ever been definitely traced to the amygdaloid area (apart from the nucleus of the lateral olfactory tract) after excision or transection of the olfactory bulb.

The olfactory tubercle in the human brain is feebly developed and often difficult to define as a " tubercle ", for it is little more than a flattened-out vestige of a relatively much larger structure in lower mammals such as the rabbit. It is essentially composed of a thin cortical formation (containing a plexiform layer of fibres superficially and, beneath this, layers of pyramidal and polymorphic cells) which overlies the rostral extremity of the caudate nucleus and globus pallidus (*see* Crosby and Humphrey, 1941). In spite of the fact that a number of observers have believed it possible to trace olfactory fibres to the olfactory tubercle in preparations of normal material, this has never been unequivocally established, and it has actually been denied by some, e.g. Cajal.

The so-called septal areas on the medial surface of the brain, which are commonly stated to receive most of the fibres of the medial root of the olfactory tract, need not be discussed in detail. They are made up of a

number of nuclear groups which have been variously defined and which occupy the pre- and post-commissural parts of the septal grey matter. As will be seen, no certain evidence was obtained from our experiments that these septal areas have any *direct* fibre connexion with the olfactory bulb.

Methods.

In eight rabbits the right olfactory bulb was resected, with the usual aseptic precautions, under nembutal anæsthesia. The bulb was exposed by the removal of a small part of the frontal region of the skull roof and incision of the dura mater. Hæmorrhage following the removal of the bulb was slight and readily controlled. No signs of infection followed the operations and recovery in all cases was uneventful. The animals were killed with an overdose of nembutal two, three, four or seven days after operation. The brain (including the remaining olfactory bulb) was removed immediately after death and fixed in 5 per cent. formol saline. After twenty-four hours each brain was cut into transverse or sagittal slices and allowed to remain in the formol saline for at least a week. For the demonstration of degenerating fibre terminals, and also of degenerating unmyelinated fibres, Bielschowsky's ammoniacal silver method and the silver method recently described by Glees (1946) were used. In addition, some sections were stained with cresyl violet in order to allow the precise localization of nuclear groups. All these methods were used on frozen sections.

For our main purpose (the demonstration of degenerating terminals and unmyelinated fibres) Glees' method was found to be superior to that of Bielschowsky. Although in our experience it does not show the finest morphological details of the *normal* terminals and terminal plexuses as seen in a successful Bielschowsky preparation, it does show up the early degenerative changes to much better effect.

The vagaries of silver-staining are well known, and the fibres of the olfactory system (particularly the olfactory nerves themselves) seem unusually refractory to successful impregnation. Our findings were evaluated with the greatest care. Each region under examination was compared first with the unoperated side of the same brain, and also with the same region of an entirely normal rabbit's brain which had been fixed and stained under exactly the same conditions as the operated cases. Only when a massive degeneration of terminals, pre-terminals or unmyelinated fibres was found, and when this was observed to be followed in other experiments after a longer time interval by an actual loss of fibres in the same region, have definite conclusions been drawn. The presence in a

region of an isolated fibre apparently undergoing degeneration, or of isolated argentophil masses resembling degenerating terminals on nerve cells, has not been taken into consideration; such appearances may in some cases be due to an erratic action of the silver salt, which may thus lead to illusory results. However, the massive degeneration of fibre terminals which we have observed in many of our preparations a few days after removal of the olfactory bulb is such a striking and clear-cut phenomenon that, when it does occur, it provides quite conclusive and precise evidence of terminal connexions (*see*, for example, Pl. X, figs. 1b and 2b). This method, therefore, is particularly favourable for obtaining positive results in an investigation of this kind. On the other hand, the absence of massive degeneration in a certain region of the brain following the interruption of afferent fibres does not necessarily mean that none of the fibres terminate there; this may be so, but it may also be the case that the terminal fibres are too insignificant in number to produce a visible result by this particular technique.

Observations.

It is convenient to describe most of the degenerative phenomena seen in our experimental material by reference to a representative series of transverse sections of the brain extending throughout the course of the olfactory tract. The results as a whole will then be summarized in a general discussion.

Section 1. (*At the level of the posterior part of the anterior olfactory nucleus.*)

At this level the lateral olfactory tract covers the entire lateral surface of the olfactory peduncle. Ventrally, however, it loses its clear-cut outline and is here composed of loosely-arranged fascicles which can be seen streaming dorsally towards the anterior olfactory nucleus and the anterior limb of the anterior commissure. Ventro-medially, the olfactory tract fibres become again more compactly arranged to form a thickened bundle —the so-called medial olfactory tract. There is, however, no sharp demarcation between this and the lateral olfactory tract.

Three days after ablation of the olfactory bulb, large degenerating fibres are seen between the lateral olfactory tract and the anterior commissure. This seems to indicate an exchange of fibres at this level, but the proximity of the lesion makes it difficult to exclude direct traumatic effects. Collaterals of the tract fibres are also seen to be breaking up among the cells of the pars externa of the anterior olfactory nucleus, and deeply

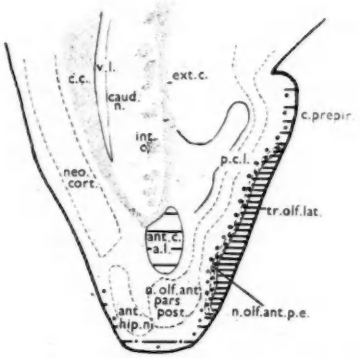
stained degenerating terminals are present here in large numbers. A similar picture (but representing a more advanced stage of degeneration) is observed in a seven-day experiment; here degenerating olfactory fibres (or their collaterals) are distinctly seen leaving the olfactory tract and entering the pars externa of the anterior olfactory nucleus. On the other hand, the fibre plexus of the anterior olfactory nucleus itself appears to be intact.

Section 2. (*At the level of the prepiriform area, the caudal end of the anterior olfactory nucleus, and the anterior hippocampal nucleus.*) *Text-fig.* 1.

In this section (as in others of the prepiriform cortex) many fine fibres from the plexiform layer of the prepiriform cortex can be seen entering the most dorsal part of the layer of olfactory tract fibres (near the rhinal sulcus) and intermingling with them. The olfactory fibres here are collaterals of the main lateral olfactory tract, which pass up towards the rhinal sulcus. Ventrally the lateral olfactory tract gradually thins out towards the basal aspect of the olfactory peduncle until it finally disappears at the level of the anterior hippocampal nucleus (text-fig. 1). The pyramidal cell layer of the prepiriform cortex merges with the caudal end of the anterior olfactory nucleus. Two days after removal of the olfactory bulb, fine rings and beading are occasionally seen in the dorsal collaterals of the olfactory tract, but they are by no means conspicuous. In a three days' experiment on an immature rabbit six weeks old (in which the degeneration was found to be more advanced than in a mature animal after the same time interval), terminal and fibre degeneration was found to be most severe in the most superficial layer of the prepiriform cortex (i.e. the layer of dorsal collaterals of the olfactory tract). Degenerating terminals and fine collaterals are also to be seen among the cells of the pars externa of the anterior olfactory nucleus adjacent to the lateral olfactory tract. After seven days, the dorsal collaterals of the olfactory tract are in an advanced stage of degeneration, and even under a low magnification it is apparent that the entire fascicle is shrunken (Pl. X, fig. 1b). Under a high magnification few degenerating terminals are to be seen, but many of the fibres have disappeared or are in process of disintegration. Degenerating fibres are also present among the normal collaterals or dendrites which form the plexiform layer of the prepiriform cortex. There is no clear sign of terminal or fibre degeneration in the pyramidal cell layer of the cortex, and no evidence of terminal or fibre degeneration is to be found in the anterior hippocampal nucleus.

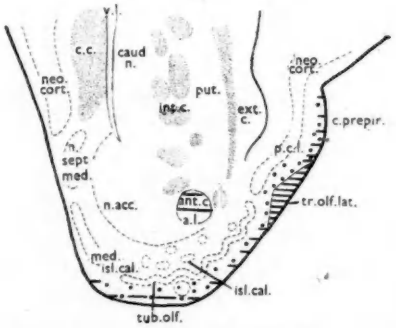
Section 3. (At the level of the olfactory tubercle and septal area.) Text-fig. 2.

After two days the increase of visible terminals in the fibre layer and the plexiform layer of the prepiriform cortex (as compared with the normal side) is quite definite, and this is taken to indicate incipient degeneration. The most superficial layer of the olfactory tubercle is formed by a dense



1.—Tracing of a transvere section through the olfactory region of the brain at the level of the posterior part of the anterior olfactory nucleus. × 10.

In this and the other text figures the distribution of axonal degeneration is shown by horizontal lines, and of terminal degeneration by coarse dots. A list of the abbreviations used in all the text-figures is given on p. 327.



2.—Transverse section at the level of the olfactory tubercle. × 10.

network of fibres, and among the latter are many degenerating terminals (quite similar in appearance to those already observed in the same layer of the prepiriform cortex). After three days there is widespread degeneration among the dorsal collaterals of the lateral olfactory tract, and

terminals appear as conspicuous argentophil masses which can clearly be seen under low magnifications. They are limited to the superficial levels of the plexiform layer of the prepiriform cortex. Dorsally, towards the rhinal sulcus, the degenerating terminals become more sparse, and finally disappear before the sulcus is reached. The superficial layer of the olfactory tubercle shows a less intense degeneration than the prepiriform cortex, but it is at the same stage of development. After four days, however, some degenerating terminals and fibres are seen quite deeply within the tubercle, a few penetrating into the pyramidal cell layer and into some of the islands of Calleja. After seven days the degenerative phenomena are all more pronounced; there are no degenerating terminals left, and the fibre disintegration is more conspicuous. Degenerating fibres are seen deep within the plexiform layer of the olfactory tubercle, and occasionally within the more superficially placed islands of Calleja. In some regions, also, disintegrating argentophil masses are seen in contact with the cells of the pyramidal cell layer. No certain evidence of terminal degeneration could be detected in the septal area.

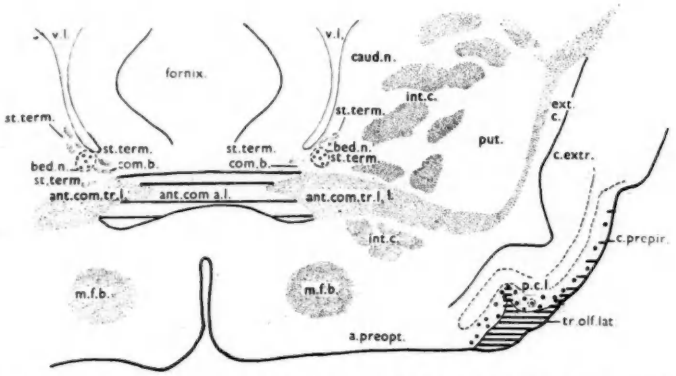
Section 4. (*At the level of the crossing of the anterior commissure and the preoptic area.*) *Text-fig. 3.*

At this transverse level the bed nucleus of the stria terminalis appears for the first time, lying in the triangle formed by the caudate nucleus, internal capsule and anterior commissure. In the three days' experiment, the degeneration in the prepiriform cortex has the same appearance as at more anterior levels, with a fascicle of degenerating fibres passing towards the pyramidal cell layer. Degenerating fibres are also evident in the olfactory component of the anterior commissure, but they are few in number and are dispersed through the whole thickness of the commissure. The bed nucleus of the stria terminalis shows bilateral preterminal fibre degeneration confined mainly to the centre of the nucleus. After seven days, the bed nucleus shows a very advanced degeneration of the terminal plexuses, with evident loss of fibres. The stria fibres themselves (cut obliquely in this section) appear to be intact.

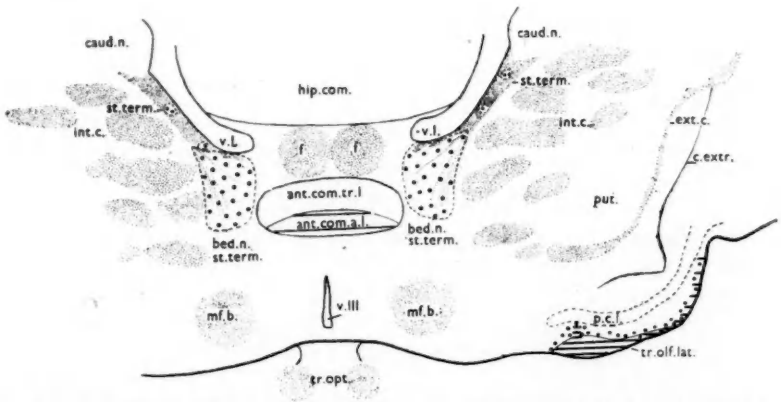
Section 5. (*At the level of the caudal part of the crossing of the anterior commissure.*) *Text-fig. 4.*

At this level, the bed nucleus of the stria terminalis reaches its greatest dimensions as seen in transverse sections of the brain. Seven days after removal of the olfactory bulb, large numbers of degenerating fibres are seen in the ventral portion of the anterior commissure, indicating the locali-

zation here of its olfactory component. It is of interest to note that in one animal in which the anterior extremity of the anterior olfactory nucleus had probably been involved by the experimental lesion, the degeneration in the decussation of the anterior commissure was found to be much more extensive than in two rabbits (also seven-day experiments) in which the



3.—Transverse section at the level of the crossing of the anterior commissure. × 10.



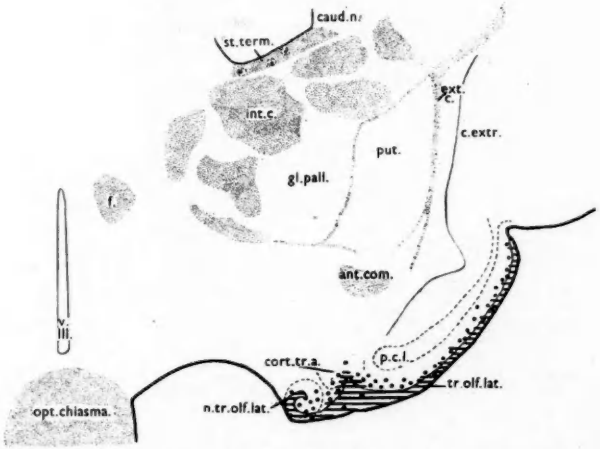
4.—Transverse section at the level of the caudal part of the crossing of the anterior commissure. × 10.

most caudal portion of the olfactory bulb had not been removed (thus probably leaving the anterior olfactory nucleus intact). The distribution of degenerating fibres in the anterior commissure at different levels makes

it clear that the olfactory component occupies its anterior and ventral sectors. The bed nucleus of the stria terminalis shows a bilateral preterminal degeneration and loss of fibres which is best seen in the small islands of cells lying among the dorsal fibres where the fascicles of the stria are collected into one bundle. Some degenerating fibres are present among the stria fascicles, but these are fine and in process of a " drop-like " disintegration resembling a preterminal or terminal plexus degeneration rather than the degeneration of tract fibres. It is concluded, therefore, that the degenerating fibres among the fascicles of the stria belong to the bed nucleus rather than to the stria itself.

Section 6. (*At the level of the prepiriform cortex and the nucleus of the lateral olfactory tract.*) *Text-fig. 5.*

At this level, the fibres of the main bundle of the lateral olfactory tract are spreading out over the surface of the piriform lobe. Ventromedially,



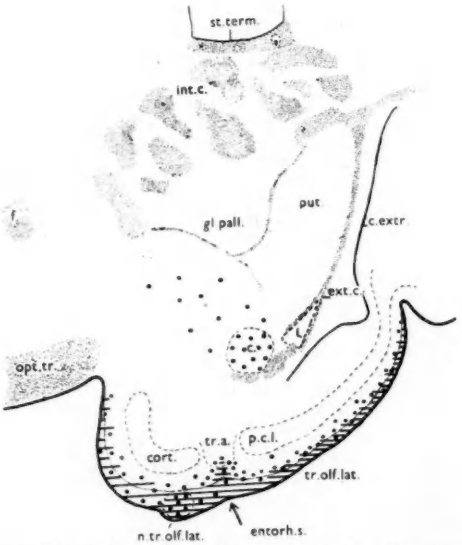
5.—Transverse section at the level of the nucleus of the lateral olfactory tract. × 10.

in the position of the anterior end of the entorhinal sulcus, a bundle of fine fibres turns in from the tract and passes towards the anterior amygdaloid area. Further medially, other fibres sweep round the nucleus of the lateral olfactory tract and appear to terminate within it. Between this nucleus and the medial border of the piriform cortex is a diffuse group of cells which has been referred to by some authors as the " cortical transition area." Three days after removal of the olfactory bulb, the degeneration

in the olfactory tract and the plexiform layer of the prepiriform cortex is similar to that observed at more anterior levels. Degenerating fibres can also be followed for some distance into the cortical transition area, and in the latter are some degenerating terminals. Degenerating terminals and fibres are present in considerable numbers in the nucleus of the lateral olfactory tract, but they are predominantly confined to that part of the nucleus immediately adjacent to the entering olfactory fibres.

Section 7. (*At the level of the anterior end of the amygdaloid complex.*) *Text-fig. 6.*

At this level, the cortical amygdaloid nucleus and the posterior part of the nucleus of the lateral olfactory tract are seen. The central nucleus



6.—Transverse section at the level of the anterior end of the amygdaloid complex. × 10.

also appears as a terminal enlargement of the bed nucleus of the stria terminalis, and the lateral element of the amygdaloid complex is beginning to show itself. Three days after removal of the olfactory bulb, degeneration is marked in the fibre and plexiform layers which cover the prepiriform cortex and the cortical amygdaloid nucleus. The terminal relationship of the olfactory fibres in these elements thus appears to be formed by axo-dendritic contacts. It is otherwise for the nucleus of the lateral

olfactory tract and the medial amygdaloid nucleus (as seen in more caudal planes), for both these elements contain within their substance degenerating fibres and collaterals, as well as evidence of terminal degeneration. It is of interest to note that not all the fibres of the lateral olfactory tract situated medial to the entorhinal sulcus are undergoing degeneration, and the tract itself in this region contains many normal fibres (whereas in the lateral part of the tract covering the piriform cortex almost all the fibres degenerate after seven days). It seems certain, therefore, that the medial part of the tract does not consist entirely of fibres of bulbar origin.

In the central amygdaloid nucleus there is an apparent loss of fibres, and degenerating fibres are also to be seen; this is the case also with the bed nucleus of the stria terminalis at this level.

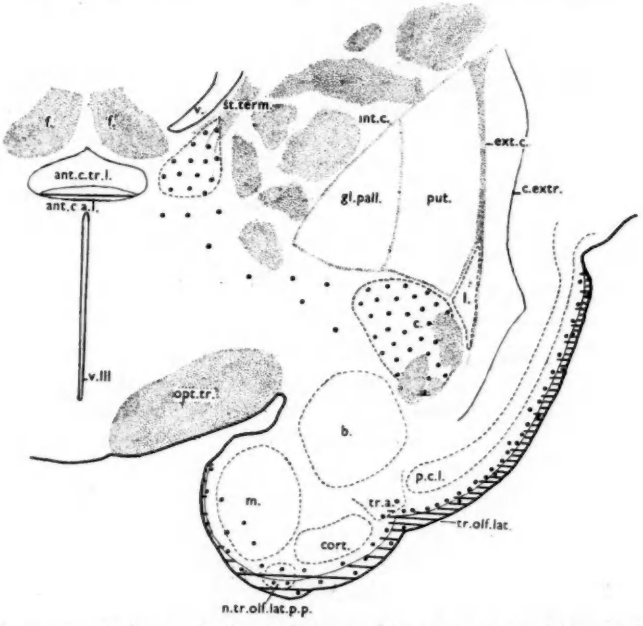
Section 8. (At the level of the anterior part of the piriform lobe and the amygdaloid complex.) Text-fig. 7.

In this section (which has been cut somewhat obliquely), the caudal margin of the crossing of the anterior commissure is still visible. Four days after the removal of the bulb, a bundle of degenerating fibres is seen entering the cortical transition area from the lateral olfactory tract. They can only be followed for a short distance. The caudal part of the medial amygdaloid nucleus (as seen in this section) is apparently reached only by very few olfactory fibres. The central amygdaloid nucleus contains many fine degenerating fibres which are even evident under a low magnification, and which also show the typical appearance of preterminal degeneration. However, not all the fibres in the nucleus are affected, and fibre bundles passing through it appear to be intact. The degenerative process seems most severe in the centre of the nucleus, gradually decreasing in intensity towards the periphery. The bed nucleus of the stria terminalis shows a bilateral degeneration of its fibre plexus which is almost complete. Fine degenerating fibres are also found among the fibre bundles of the posterior limb of the anterior commissure and scattered over an area medial to the central amygdaloid nucleus, between the latter and the bed nucleus of the stria.

Section 9. (At the level of the middle of the amygdaloid complex.) Text-fig. 8.

Three days after removal of the olfactory bulb, the dorsal part of the lateral olfactory tract and the piriform cortex show essentially the same degenerative changes as those seen at more anterior levels. Terminals are enlarged and darkly stained and fine fibres are beginning to disintegrate.

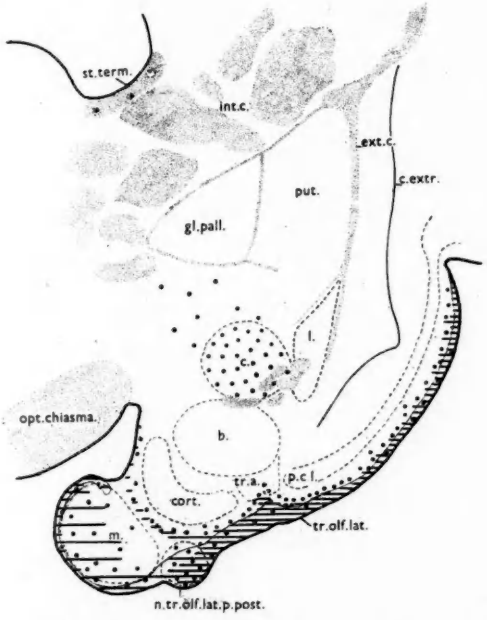
The latter are seen entering the plexiform layer of the cortex. Few degenerating fibres and terminals are found in the ventral part of the tract, but they can be traced in an unbroken series from the entorhinal sulcus as far as the lateral margin of the optic tract (*see* text-figs. 7 and 8). The nucleus of the lateral olfactory tract, pars posterior, is lying within the fibre layer, and degenerating fibres are almost surrounding the medial amygdaloid nucleus. Degenerating fibres and terminals are also seen within the medical amygdaloid nucleus and the nucleus of the lateral olfactory



7.—Transverse section at the level of the anterior part of the piriform lobe and the amygdaloid complex. × 10.

tract. In the central amygdaloid nucleus there is a commencing degeneration of the pericellular terminal plexuses on both sides of the brain; beaded and swollen fine fibres are seen encircling the cells and many fine fibres are undergoing degeneration in a characteristic " drop-like " fashion. The bed nucleus of the stria terminalis shows the same type of rather advanced bilateral fibre degeneration. No abnormal change can be detected in the lateral and basal amygdaloid nuclei, the globus pallidus or the claustrum, nor in the lateral olfactory tract and piriform cortex of the unoperated side.

After seven days the changes in the central and medial amygdaloid nuclei are still more pronounced, and many disintegrating fibres, in the form of a series of interconnected "droplets," can be followed through the whole field viewed under an oil-immersion lens. Also conspicuous at this level are the fine degenerating fibres entering the nucleus of the lateral olfactory tract, and passing in towards the amygdaloid area on either side of the nucleus.



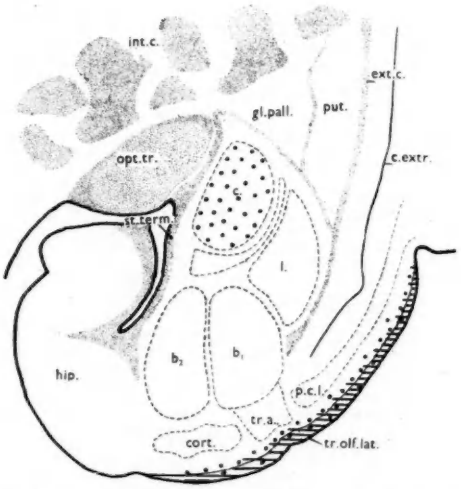
8.—Transverse section at the level of the middle of the amygdaloid complex. × 10.

Section 10. (At the level of the caudal part of the amygdaloid complex and the beginning of the hippocampal formation.) Text-fig. 9.

At this level the lateral olfactory tract extends from the rhinal sulcus to the groove separating the ventro-medial end of the cortical amygdaloid nucleus from the hippocampal formation. The cortical amygdaloid nucleus is somewhat corrugated in outline. The basal amygdaloid nucleus is composed of two groups of cells—the basal nucleus proper (easily recognizable in Nissl sections by its characteristic large and deeply stained cells), and the

small-celled accessory basal nucleus between it and the stria terminalis (*see* text-fig. 9).

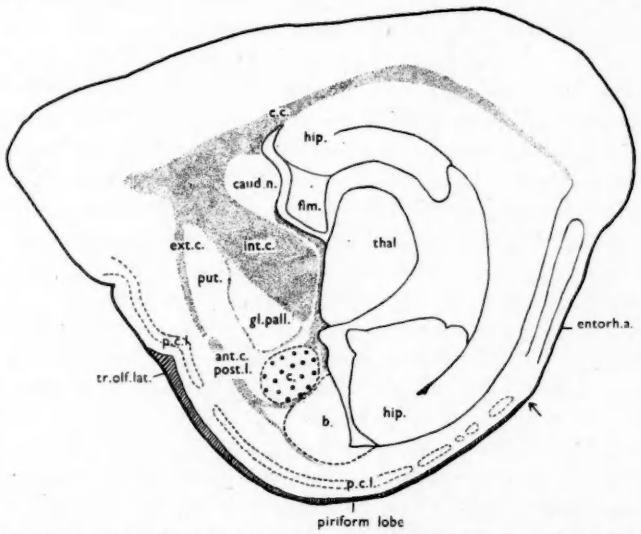
Four days after removal of the olfactory bulb, the central amygdaloid nucleus is filled with degenerating fine fibres as at more anterior levels. In the basal accessory amygdaloid nucleus are many terminals showing the same variety of appearance and size as described in the normal spinal cord by other observers (e.g. Gibson, 1937), but none of these appear to be undergoing any degenerative change. No evidence of degeneration could be found either in the lateral and basal amygdaloid nuclei, or in the hippocampal formation.



9.—Transverse section at the level of the caudal part of the amygdaloid complex. × 10.

After seven days, there is a considerable loss of fine fibres in the central amygdaloid nucleus of both sides, which is very striking even under a low magnification. Many of the remaining fibres are also in a state of disintegration, and their remnants can be seen as rings of small dots surrounding the nerve cells (Pl. XI, figs. 8c and 8d). The degenerative process stops abruptly at the circumference of the nucleus and in all the surrounding nuclei the fibre plexuses still remain quite normal. In the piriform cortex at this level, a few fine disintegrating fibres from the lateral olfactory tract may be found in the pyramidal cell layer, but the pericellular plexuses here are intact.

The degenerative changes following unilateral "leucotomy" of the frontal lobe in a rabbit.—This experiment is included in our series since the lesion involved the fibres of the anterior commissure on the operated side, but left the lateral olfactory tract intact. The animal was killed two weeks after the operation. Silver sections of the brain showed very distinct fibre degeneration in the anterior commissure and external capsule, and also in the stria terminalis (particularly the commissural and pre-optic fasciculi). Degenerated fibres of the pre-optic fasciculus of the stria terminalis are seen entering the central amygdaloid nucleus. The latter shows severe degeneration of its fibre plexus (rather more severe than that



10.—Sagittal section through the cerebral hemisphere to one side of the medial plane (for explanation, *see* text). × 5.

seen after removal of the olfactory bulb), and, indeed, very few intact fibres are left. On the other hand, the fibres of the lateral olfactory tract and the plexuses in adjoining nuclei appear to be quite normal. The central amygdaloid nucleus on the unoperated side also shows degenerative changes, though not so marked as on the side of the lesion. This experiment indicates that the olfactory fibres which reach the central amygdaloid nucleus must do so by way of the anterior commissure rather than the lateral olfactory tract. In text-fig. 10 a diagram is shown of a laterally placed sagittal section through the brain, and the resulting terminal

degeneration in the central amygdaloid nucleus is indicated. In the same diagram, the extent of the fibre degeneration in the lateral olfactory tract, following removal of the bulb in other experiments, is also shown. It should be noted that the fibres of the olfactory tract only reach as far as the margin of the entorhinal cortex (marked in the diagram by an arrow).

Degeneration in the contralateral olfactory bulb.—Three days after removal of the olfactory bulb on one side, very few clearly degenerating fibres are to be seen in the anterior limb of the anterior commissure in the opposite olfactory peduncle, and these are not confined to any particular fascicle but are evenly distributed through the tract. No degeneration is seen in any part of the anterior olfactory nucleus here. In the contralateral olfactory bulb there is distinct evidence of degeneration. It may be noted that in normal material stained by our silver method, the zone surrounding the olfactory ventricle shows a large number of normal terminals and beaded fibres such as we have not observed in any other part of the rabbit's brain, and this may be taken to indicate that the zone is normally the site of intense synaptic activity. In the experimental animals fine disintegrating fibres are observed among the normal terminals, and in some instances a typical swollen argentophil end-tube can be found in connexion with an apparently normal fibre (Pl. XI, fig. 6). In the internal granular layer of the bulb, degenerating fibres are much more frequent immediately rostral to the olfactory ventricle. The number of degenerating fibres and terminals gradually diminishes towards the internal plexiform layer of the bulb, and in the mitral cell layer, outer plexiform layer and glomeruli no degenerative change can be detected. In a seven-day experiment, the anterior commissure in the contralateral olfactory peduncle shows quite distinctly fine degenerating fibres, though these are relatively few in number. The anterior olfactory nucleus remains free of any sign of fibre degeneration. In the opposite bulb, a considerable number of fine degenerating fibres are present in the internal granular layer within a network of normal fibres, and some can be followed into the external plexiform layer. No degenerating terminals or preterminals can be detected surrounding the mitral cells. Some degenerating fibres, however, can be followed *through* the layer of mitral cells, and a few are to be seen in the external granular layer between the glomeruli. None can be certainly detected within the glomeruli.

Discussion.

Our experimental material has provided unusually satisfactory and convincing evidence regarding the precise site of termination of fibres from

the olfactory bulb, and has cleared up a number of uncertainties which have existed for many years. In this discussion, we propose to deal separately with the main terminal stations of the olfactory tract.

The olfactory tubercle.—This tubercle consists essentially of three layers—the superficial fibre or plexiform layer, a pyramidal cell layer and a polymorphic cell layer. Cajal (1901), in Marchi material, was unable to find degenerated fibres in the tubercle after extirpation of the olfactory bulb. Elliot Smith (1909) found degeneration in the lateral half of the tubercle in marsupials. Fox, McKinley and Magoun (1944), in an oscillographic study in the cat, recorded responses from the surface of the tubercle after stimulation of the olfactory bulb, while Rose and Woolsey (1943) were unable to do so. In our experiments distinct degeneration of terminals, followed later by a loss of fibres, was found in the plexiform layer of the tubercle and, in a few instances, around nerve cells and within the islands of Calleja. The degeneration is less massive than in the prepiriform cortex, and it is more marked in the lateral and ventral part of the tubercle, diminishing and gradually disappearing as the posterior and medial sectors are approached. This terminal degeneration thus makes it clear that the olfactory tubercle receives either direct bulbar fibres, or at least collaterals from the lateral olfactory tract.

Prepiriform cortex.—Cajal divides the prepiriform cortex into several layers. The first contains fibres and collaterals of the lateral olfactory tract, the second (or plexiform) layer contains arborizations of the ascending dendrites of pyramidal cells and terminal fibres and collaterals of the olfactory tract, and the third layer contains the pyramidal cells. In our experiments, degeneration was found to be most severe in the most superficial layer and, to a lesser degree, in the superficial zone of the plexiform layer. Very few degenerating fibres were seen penetrating deeply into the plexiform layer, and they seem hardly ever to reach the pyramidal cells. Thus it appears (as Cajal has previously affirmed) that synaptic contact between the olfactory fibres and the dendrites of the pyramidal cells is mainly effected in the first and second layers, and particularly by the penetration of the dendrites into the layer formed by the collaterals of the olfactory tract (Pl. X, fig. 2a). Since signs of terminal degeneration are so rarely to be seen in the pyramidal cell layer it must be concluded that the synapses here are practically entirely axo-dendritic.

The degeneration in the fibres of the lateral olfactory tract was found to extend over the prepiriform cortex (in which most of the fibres end) and also the peri-amygdaloid cortex of the piriform lobe. Cajal's view that the anterior portion of the prepiriform area receives collaterals of the lateral

olfactory tract, and the posterior portion the terminals of these same fibres, is corroborated by our results. On the other hand, Cajal (1911) and Gray (1924) have expressed a doubt whether the peri-amygdaloid region is reached by direct olfactory fibres. Degeneration could not be traced into the entorhinal area of cortex. It is concluded, therefore, that this last part of the piriform lobe probably receives no direct bulbar fibres.

The amygdaloid complex.—There has been little or no unanimity of opinion on the question whether olfactory fibres terminate in the amygdaloid region and, if so, in which specific nuclear elements. As already noted in the introduction, many statements which have appeared in the literature concerning such connexions are based on the examination of fibre preparations of normal material, and this type of evidence is subject to many fallacies. Studies of the olfactory system by recording the changes in electrical potential which occur after stimulation of the olfactory bulb have included an exploration of the amygdaloid nucleus, but the results still remain contradictory. Fox, McKinley and Magoun (1944) reported no potentials from the amygdaloid nuclei (though, according to their diagram, potentials were recorded from the ventro-lateral part of the nucleus of the lateral olfactory tract and that part of the piriform lobe which surrounds the cortical amygdaloid nucleus). Rose and Woolsey (1943) report that responses were received from the peri-amygdaloid region. Allen (1941) studied the effects of ablating different parts of the rhinencephalon, including the amygdaloid-piriform region, on conditioned reflexes in dogs. He concluded that the amygdaloid-piriform complex is an important olfactory centre, but that it does not represent the sole centre for detecting minute differences in odour.

An evaluation of our results shows, firstly, that the cortico-medial group of nuclei (including the central nucleus) and the cortico-amygdaloid transition area of the amygdaloid complex, together with the bed nucleus (or interstitial nucleus) of the stria terminalis, receive fibres which arise in the olfactory bulb, but the baso-lateral amygdaloid group has no such direct olfactory connections. While the fibres terminating in the nucleus of the lateral olfactory tract, the medical amygdaloid nucleus, the cortical amygdaloid nucleus and the cortico-amygdaloid transition area are conveyed in the lateral olfactory tract, those to the bed nucleus of the stria terminalis and the central amygdaloid nucleus evidently reach them by way of the anterior commissure. It was also observed that the severity of the terminal degeneration in the bed nucleus and the central amygdaloid nucleus is clearly related to the extent of the bulbar lesion and to the number of degenerating fibres found in the anterior limb of the

anterior commissure. These results have a significant bearing on experiments reported by Swann (1934, 1935) on the effects of destruction of olfactory and other parts of the brain on the discrimination of odours in rats. He found that the lateral and medial olfactory tracts and up to 83 per cent. of cerebral cortex (including the hippocampus) may be removed without serious loss of performance, but that any injury to the anterior limb of the anterior commissure results in conspicuous or complete loss of learned discriminating ability. He concludes that " the assumption that this olfactory habit in the rat is of a subcortical nature is well founded."

The nucleus of the lateral olfactory tract in the rabbit is composed of two parts (as described also for Man by Crosby and Humphrey, 1941). The anterior portion (the most rostral component of the whole amygdaloid complex) receives fascicles from the lateral olfactory tract which, after partially surrounding it, enter and terminate in typical terminal swellings on its nerve cells (axo-somatic synapses). The posterior portion lies between the cortical and medial amygdaloid nuclei, and is almost embedded among the fibres of the lateral olfactory tract. It forms here a slight elevation on the surface of the piriform lobe and, following ablation of the bulb, was also found to contain degenerating fibres and terminals. In both portions of the nucleus, the terminal degeneration is most severe in the zone adjoining the lateral olfactory tract. This was also the case with the medial amygdaloid nucleus; at some levels degenerating fibres of the lateral olfactory tract almost surround this nucleus and fibres enter either singly or in fascicles to terminate on its nerve cells. The anterior part of the medial nucleus is particularly affected, but its caudal part appears to receive much fewer fibres. As regards the cortical amygdaloid nucleus, few olfactory fibres appear to make actual contact with the nerve cell bodies. Degenerating fibres and terminals are mainly seen in the superficial plexiform layer, indicating that the synaptic mechanism here is axo-dendritic and thus resembles that described for the piriform cortex and olfactory tubercle.

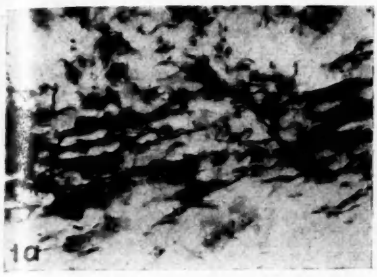
In the cortico-amygdaloid transition area, contact between the fibres of the lateral olfactory tract and the nerve cells is also axo-dendritic but, in addition, fascicles enter this area and apparently terminate there. The anterior part of the cortical transition area receives a particularly massive accession of olfactory fibres, and it is possible that it comprises a distributing centre through which olfactory impulses may be relayed to other elements of the amygdaloid complex.

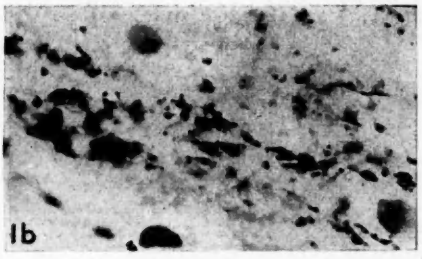
In general summary, our results indicate that the cortico-amygdaloid

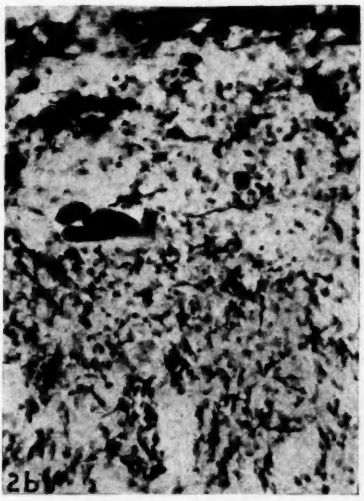
transition area and the bed nucleus of the stria terminalis must be included in the cortico-medial group of the amygdaloid complex (as defined by Johnston) and that this entire group is olfactory in function. On the other hand, we find no evidence of direct olfactory connexions with the basal and lateral amygdaloid nuclei. It is particularly interesting to note, therefore, that Crosby and Humphrey (1941) find that, compared with lower macrosmatic mammals, the baso-lateral amygdaloid group is more highly differentiated in the human brain, while the cortico-medial group is much reduced. The nucleus of the lateral olfactory tract and the medial nucleus are particularly poorly developed in Man.

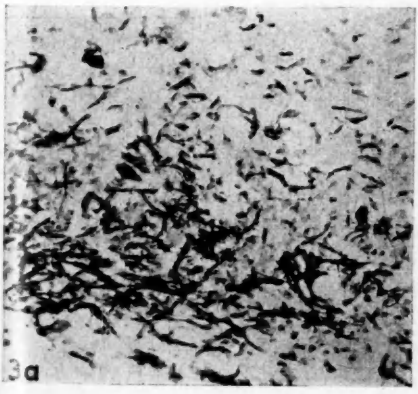
The termination of the olfactory component of the anterior commissure in the contralateral olfactory bulb.—Cajal (1911) concluded that fibres of the anterior commissure arise in the olfactory bulb from outlying mitral cells (his " cellules à panaché") and terminate in the opposite bulb on the dendrites of the cells of the internal granular layer. Probst (1901) also followed degenerating fibres into the opposite bulb and in his Marchi experiments described osmic granules around the olfactory ventricle. Edinger (1908) similarly traced interbulbar fibres into the internal granular layer of the opposite bulb. Elliot Smith (1909), van Gehuchten (1904) and Loewenthal (1897) do not agree with these findings. According to their results, degeneration in the contralateral bulb can only be demonstrated when the primary lesion includes part of the olfactory lobe behind the bulb. Recently, Young (1942) has concluded that "interbulbar" fibres really take origin and terminate in the anterior olfactory nucleus, and since he regards this nucleus as a rostral extension of the piriform cortex he suggests that the anterior part of the anterior commissure is to be regarded as a cortical commissure interconnecting the prepiriform cortex of both sides. Our own experiments are perhaps too limited to give a final answer to all the questions involved. In two of our experimental lesions the caudal portion of the olfactory bulb was left intact, and in one case the caudal part of the internal granular layer rostral to the olfactory ventricle was not removed. It is hardly possible to say with certainty how far the anterior olfactory nucleus may have been indirectly affected in these experiments by trauma, but our sections have shown that the traumatic effect of the lesions involving the bulb were usually remarkably localized. It is true that in these cases relatively few fibres of the anterior commissure were found to be degenerated, but there was a severe degeneration of terminals and preterminals mainly in the internal granular layer of the opposite bulb. On the other hand, no degeneration or fibre loss was seen in any part of the anterior olfactory nucleus of the opposite side, an observation which is not in accord with Young's suggestion.

PLATE X









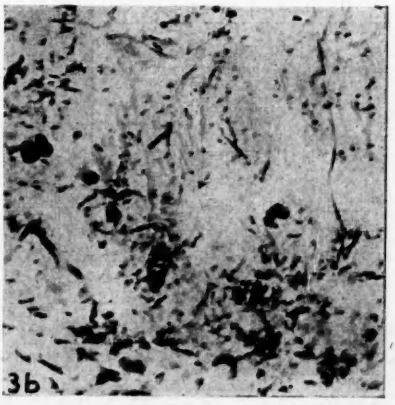
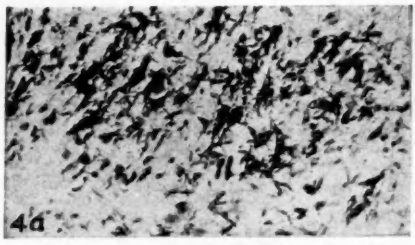
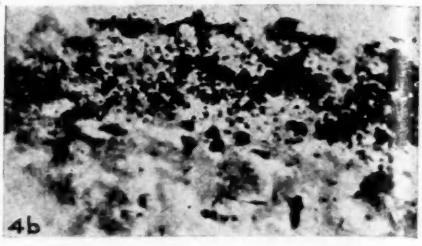


PLATE XI


4a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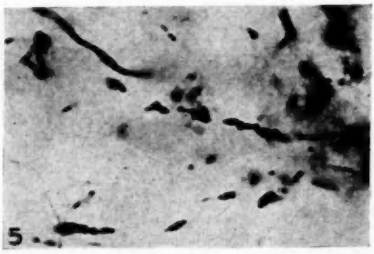
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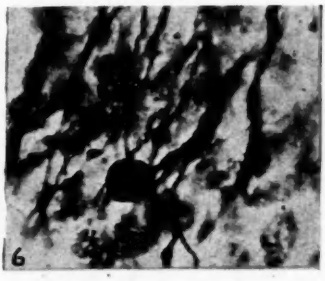
6

7

8a

8b

8c

8d

The significance of the degenerating fibres occasionally seen passing through the mitral cell layer and into the external granular and plexiform layers of the opposite bulb is by no means clear, for no definite *terminal* degeneration could be found in these layers. From our series of experiments we can only conclude that, after removal of the anterior two-thirds of the olfactory bulb, degeneration of the terminals and preterminal fibres of the anterior portion of the anterior commissure in the contralateral bulb is seen mainly in the internal granular layer.

The relation of the olfactory bulb to the septal areas.—One of the surprising results of our experiments has been the absence of any distinct sign of fibre or terminal degeneration in the septal areas of the brain. Since it is commonly stated that the "medial root" of the olfactory tract terminates in this region, we have, of course, examined it very carefully in our histological sections. The consistent absence of degenerative change here compels the conclusion that the septal areas receive no direct afferent connections from the olfactory bulb. If they receive olfactory impulses these must presumably be relayed in the grey matter of the olfactory peduncle or elsewhere. Our material also indicates that in the rabbit there is in fact no sharp division of the olfactory tract into different "roots." The tract is mainly applied to the lateral surface of the olfactory peduncle and prepiriform cortex where it forms what is usually termed the "lateral olfactory tract." Ventro-medially in transverse sections it gradually thins out over the olfactory tubercle and the amygdaloid complex until it finally fades and disappears at the medial margin of these regions. In the most anterior sections, a slight thickening of the layer of olfactory tract fibres at its medial margin may be interpreted as a "medial olfactory tract," but this does not remain recognizable as a definite part of the whole tract system in more caudal levels. We may emphasize, also, that in no experiment were degenerated fibres or terminals found in the anterior hippocampal nucleus or in any part of the hippocampal formation.

We wish to express our thanks to Miss P. L. Plumbridge for her skill in the preparation of the diagrams and to acknowledge with gratitude the expenses grant made to one of us (M. M.) from the Maudsley Bequest.

SUMMARY.

(1) The connexions of the olfactory tract in the rabbit's brain have been studied experimentally, after removal of the olfactory bulb, by the demonstration of terminal degeneration.

(2) The lateral root of the olfactory tract terminates in a limited part of the cortex of the piriform lobe—the prepiriform area and the peri-

amygdaloid cortex. No fibres can be traced to the entorhinal area or the hippocampus.

(3) Olfactory fibres terminate in the cortico-medial group of amygdaloid nuclei, but not in the baso-lateral group. Those reaching the central amygdaloid nucleus and the bed nucleus of the stria terminalis appear to do so by way of the anterior commissure.

(4) Terminal degeneration is present in the olfactory tubercle after removal of the olfactory bulb.

(5) No definite evidence of terminal degeneration could be established in the septal area in any of the experiments.

(6) Following lesions in one olfactory bulb, terminal degeneration is found in the contralateral bulb mainly in the internal granular layer.

REFERENCES.

ALLEN, W. F. (1941), *Am. J. Physiol.*, **132**, 81.

BRODAL, A. (1947), *Brain*, **70**, 179.

CROSBY, E. C., and HUMPHREY, T. (1941), *J. Comp. Neurol.*, **74**, 309.

EDINGER, L. (1908-11), *Vorlesung über den Bau der nervösen Centralorgane des Menschen und der Thiere*, Leipzig.

ELLIOT SMITH, G. (1909), *Anat. Anz.*, **34**, 200.

FOX, C. A. (1943), *J. Comp. Neurol.*, **79**, 277.

—— MCKINLEY, W. A., and MAGOUN, H. W. (1944), *J. Neurophysiol.*, **7**, 1.

—— and SCHMITZ, J. T. (1943), *J. Comp. Neurol.*, **79**, 297.

GEHUCHTEN, A. VAN (1904), *Le Névraxe*, **6**, 193.

GIBSON, H. C. (1937), *Arch. Neurol. Psychiat.*, **38**, 1145.

GLEES, P. (1946), *J. Neuropath. and Exper. Neurol.*, **5**, 54.

GRAY, P. A. (1924), *J. Comp. Neurol.*, **37**, 221.

HUMPHREY, T. (1936), *J. Comp. Neurol.*, **65**, 603.

JOHNSTON, J. B. (1923), *J. Comp. Neurol.*, **35**, 337.

LOEWENTHAL, S. (1897), *Braunschweig.*, pp. 213.

PROBST, M. (1901), *Arch. Anat. Physiol.*, **23**, 336.

RAMON Y CAJAL (1901), *Trab. de lab. de invest. biol. Univ.* Madrid, **2**, 82.

—— (1911), "Histologie du Système Nerveux de l'homme et des Vertebrés," Vol. 2. Paris.

ROSE, J. E., and WOOLSEY, C. N. (1943), *Fed. Proc. Amer. Soc. exp. biol.*, **2**, 42.

SWANN, H. G. (1934), *J. Comp. Neurol.*, **59**, 175.

—— (1935), *Am. J. Physiol.* **3**, 257.

YOUNG, M. W. (1936), *J. Comp. Neurol.*, **65**, 295.

—— (1942), *Anat. Rec.*, **82**, 480.

ABBREVIATIONS IN TEXT FIGURES.

A. preop.	=	Area preoptica.
Ant. c. a. l.	=	Anterior commissure, anterior limb.
Ant. c. tr. l.	=	Anterior commissure, transverse limb.
Ant. hip. n.	=	Anterior hippocampal nucleus.
Bed n. st. term.	=	Bed nucleus of stria terminalis.
C. extr.	=	Capsula extrema.
Caud. n.	=	Caudate nucleus.
C.	=	Central amygdaloid nucleus.
C.C.	=	Corpus callosum.
C. prepir.	=	Cortex prepiriformis.
Cort.	=	Cortical amygdaloid nucleus.
Cort. tr. a.	=	Cortical transition area.
Entorh. a.	=	Entorhinal area.
Entorh. s.	=	Entorhinal sulcus.
Ext. c.	=	External capsule.
Fim.	=	Fimbria.
f.	=	Fornix.
Gl. pall.	=	Globus pallidus.
Hip. com.	=	Hippocampal commissure.
Int. c.	=	Internal capsule.
Isl. Cal.	=	Islands of Calleja.
M.	=	Medial amygdaloid nucleus.
Med. isl. Cal.	=	Medial islands of Calleja.
M.f.b.	=	Medial fore-brain bundle.
Neo. cort.	=	Neo-cortex.
N. acc.	=	Nucleus accumbens.
N. olf. ant. p. e.	=	Nucleus olfactorius anterior, pars externa.
N. olf. ant. p. post.	=	Nucleus olfactorius anterior, pars posterior.
N. tr. olf. lat.	=	Nucleus tractus olfactorius lateralis.
Put.	=	Putamen.
P. c. l.	=	Pyramidal cell layer of prepiriform cortex.
St. term.	=	Stria terminalis.
Thal.	=	Thalamus.
Tr. olf. lat.	=	Tractus olfactorius lateralis.
Tr. opt.	=	Tractus opticus.
Tub. olf.	=	Tuberculum olfactorium.
V. l.	=	Ventriculus lateralis.
V. III.	=	Ventriculus tertius.

PLATE X

All the Plate figures are Microphotographs of Silver Sections.

1*a*.—The appearance of normal fibres of the lateral olfactory tract seen on the surface of the anterior part of prepiriform cortex. × 800.

1*b*.—Degenerating fibres and loss of fibres seen in the corresponding area seven days after removal of olfactory bulb. × 800.

2*a*.—Normal fibres of the lateral olfactory tract over the anterior part of the prepiriform cortex (at the level of the olfactory tubercle). Above is seen the tract itself, and below the fibres of the tract entering the plexiform layer of the prepiriform cortex. × 600.

2*b*.—Degeneration of terminals, with many fibres still preserved, in the corresponding area three days after removal of olfactory bulb. × 600.

3*a*.—The appearance of the superficial layers of the normal olfactory tubercle. × 450.

3*b*.—Degeneration with loss of fibres in the olfactory tubercle seven days after removal of the olfactory bulb. × 450.

PLATE XI

4*a*.—The appearance of the normal lateral olfactory tract as it spreads out over the prepiriform cortex. × 400.

4*b*.—Débris of fibres of the lateral olfactory tract seen in the corresponding area seven days after removal of the olfactory bulb. × 400.

5.—High power view of degenerating fibres in the olfactory tubercle seven days after removal of the olfactory bulb. × 1,000.

6.—The degenerating terminal of a fibre of the anterior limb of the anterior commissure seen near the olfactory ventricle in the olfactory bulb seven days after removal of the opposite bulb. × 1,400.

7.—Degenerating fibres from the lateral olfactory tract seen entering the nucleus of the lateral olfactory tract seven days after removal of the olfactory bulb. × 800.

8*a*.—The appearance under high power of the normal central amygdaloid nucleus. × 1,500.

8*b* and 8*c*.—Degeneration of fine fibres within the central amygdaloid nucleus four days after removal of the olfactory bulb. × 800.

8*d*.—Degeneration (drop-like distintegration) of the pericellular plexus and loss of fibres in the central amygdaloid nucleus seven days after removal of the olfactory bulb. × 1,500.

ON THE ROLE OF THE PYRAMIDAL SYSTEM IN WILLED MOVEMENTS[1]

BY

F. M. R. WALSHE.

(1) Some General Principles of Study.
(2) Hemiplegia as a Basis for the Study of Pyramidal Function.
  (i) The Dual Character of Hemiplegia.
  (ii) The Loss of Willed Movements in Hemiplegia.
    (*a*) Pyramidal Lesion in Monkey and Chimpanzee.
    (*b*) Defect and Loss of Willed Movements in Clinically Observed Hemiplegia.
(3) The Role of the Pyramidal System in Willed Movements.
  (i) The Relation of Pyramidal System to Motor Cortex.
  (ii) The Relation of Pyramidal System to Subordinate Motor Mechanisms.
  (iii) The Relation of Pyramidal System to Musculature.
(4) Summary.

> *"In dealing with theoretical considerations concerned with the physiology of the nervous system, one is exceptionally liable to be misled by preconceived or introspectively evolved notions. . . . Symmetry and the desire for classification are apt to be mistaken for physiological principles and we tend to drift into the error of supposing that conceptions that are clear-cut, easily comprehensible and 'reasonable,' acquire by that very fact an increased probability of being accurate expositions of the physiological processes they profess to explain . . . physiological necessity is apt to defy our preconceived notions of reasonableness and to escape any classification which is more respectful of logic than of fact."*
>
> (*Wilfred Trotter*, 1913, *Jour. f. Psychol. u. Neurol.*, 20, 123.)

THAT before a gathering of physicians, I should propose to deal with the physiology of the pyramidal system may seem to call for some apology from me, yet though what I shall have to say may well be of less importance than this meeting deserves, the choice itself can, I submit, be justified.

It is in the tradition of clinical neurology that it should maintain the closest association with the physiological study of the nervous system, and many are the noteworthy contributions to this science that clinical ob-

[1]A Paper read in abridged form before the Neurological Section of the International Conference of Physicians, London, September, 1947.

servation has made. Yet there is a special justification for considering the role of the pyramidal system in willed movements, namely, that the human subject provides better opportunities for this study than does the animal in the experimental laboratory.

This may seem a surprising view, so modestly have we come to think of the clinical method in our time, but I am fortified in my belief by the following circumstance. When, recently, I began to put my ideas upon this subject in order, I ventured to mention my proposal to Sir Charles Sherrington who replied to me "you choose a hard question, and one which the bedside is far better placed to solve than is the laboratory, I think. The pyramidal system is such a human feature." Thereupon he elaborated this theme with that insight into neural function we have come to regard as peculiarly the gift of this great physiologist.

There remains yet another advantage in the choice of the human subject and the clinical method: namely, that any study of disorders of willed movement from pyramidal lesion demands from the patient a degree of co-operation that no animal affords.[1]

These considerations, therefore, and others as good that could be adduced, are my apology for my subject to-day. It remains to ask how the problem is to be tackled. As clinicians we turn naturally to the observed phenomena of normal movement, and then to those of hemiplegia as the classic expression of pyramidal deficit: embracing in our survey hemiplegias of every degree of severity, hemiplegia with and without associated changes in muscle tone, hemiplegias from cortical and from subcortical lesions: developing hemiplegia and recovering hemiplegia and so on. Again, we shall have to consider the recorded results of animal experiments: of cortical stimulations and ablations, and of sections of the medullary pyramid.

Definition of the Terms "Pyramidal" and "Extrapyramidal" as Applied to Neurone Systems.

There can be few terms in neuro-anatomy and neuro-physiology more in need of precise definition. A number of assumptions has grown up around both, the tacit acceptance of which has confused many a physiological exposition. Thus it was long taught that the pyramidal tract arose exclusively from the Betz or giant cells of the precentral convolution, and that the cells so named possessed an

[1]For example, Sarah Tower (1940) speaks of "the limits set upon minuteness of examination by the unco-operative monkey," and again (1944) she notes that the hemiplegic chimpanzee after pyramidal lesion "is extraordinarily unstable in mood, swinging from unmanageable unco-operativeness to equally unmanageable co-operativeness."

anatomical and physiological specificity.[1] Both assumptions are now at last dispelled, and, in their fall, have swept away those physiological hypotheses of motor cortical function which depended for a foundation upon their reality. This aspect of the problem of the identity of the pyramidal system has already been discussed by me elsewhere (Walshe, 1942*b*), while Tower (1944) has summarized the latest details of the origin and constitution of the pyramidal tract. It is not necessary, therefore, to cover this ground anew. What is here referred to as the pyramidal system are those corticospinal fibres which arise from pyramidal cells in the fifth layer of the precentral cortex, and, traversing the medullary pyramid, decussate or remain uncrossed and make up the crossed and uncrossed pyramidal tracts respectively of the spinal cord. It is possible that these fibres in their course from cortex to medullary pyramid give off collaterals which establish anatomical connexions and physiological relations with subcortical masses of grey matter. If this is so, then the pyramidal system below the medullary pyramid has a more restricted constitution than it has at higher levels.

It might follow from this that variations in range of function are involved: the higher part of the pyramidal system which contains fibres in addition to those which are corticospinal having a wider physiological role than that subserved by the latter fibres which constitute the medullary pyramid and the pyramidal tracts of the cord. To mention these possibilities is to indicate the incompleteness of our knowledge, not only of the physiology but even of the anatomy of the pyramidal system.

The term "extrapyramidal" though of comparatively modern origin has also had its vicissitudes, its referents being so often changed that it is now necessary to define it upon each occasion of use. In his classic paper on progressive lenticular degeneration, Kinnier Wilson used the term in connection with both afferent and efferent pathways including a cerebello-rubro-thalamo-cortical and a lenticulo-rubro-spinal path within the category of extrapyramidal pathways. In the early years of the century, Rothman appears to have used it for paths efferent from the cerebral cortex other than the pyramidal, but later, the term became restricted to certain subcortical efferent systems, namely, the basal ganglia and their projection paths. Its renewed extension to refer to pathways arising in, and efferent from, the precentral region of the cortex is a more recent development. *In the present paper the term "extrapyramidal" refers to efferent cortical neurone systems other than the pyramidal, and also to all subcortical efferent neurone systems, that subserve movement.*

(1) Some General Principles of Study.

Before we plunge *in medias res* and proceed to consider the relevant clinical and experimental data, let us for a few moments dwell upon some general principles that should govern our approach to the problem before us.

Whether of clinical or experimental origin our data are in large part the results of lesions of the nervous system, and it is essential to appreciate

[1]It is interesting to note that as long ago as 1881, Bevan Lewis, the pioneer of cortical cytoarchitectonics, expressed the view that the "giant cells" described by Betz did not constitute a specific morphological category, but were merely the largest representatives of a general formation of cells of wider distribution than Betz affirmed (cf. *Brain*, 4, 238).

at the outset that the determination of normal function from the study of the symptoms of lesions is a very complex affair. The failure to grasp this underlies the many unsatisfactory hypotheses of nervous function that obtain currency. If, for example, tremor ensues upon a focal and destroying lesion of some part of the brain, we may not conclude that the function of the part destroyed was to inhibit tremor. It might be thought that no one would propose so naïve an hypothesis, but it is precisely this idea that was invoked by Ramsay Hunt (1917) to account for the tremor of the Parkinsonian syndrome. Nor was he in any way unique in his point of view, for speculations of this order abound in neurological literature in respect of many encephalic structures and their functions.

Many of us can recall those analyses of cerebellar ataxy that were current in the early years of this century, which proposed, on the one hand, that the atonia and asthenia of cerebellar ataxy were due to loss of a normal tonic or sthenic action of the cerebellum upon neuromuscular activity, while on the other hand, the overshooting of the mark by the hand and arm of the ataxic subject when he stretched out to grasp some object, the so-called dysmetria, was attributed to the loss of a normal "braking" action of the cerebellum upon the same neuromuscular activity.

Nothing, indeed, could be easier than this facile *ad hoc* creation of a fresh function to explain each manifestation of disordered movement revealed by each different clinical test, but it is not physiology.

The inadequacy of the kind of symptom interpretation we have been discussing may perhaps be most clearly illustrated by a mechanical analogy, as apt in its way as an analogy can be. In the transmission system of a motor car, two toothed and bevelled wheels engage at right angles. If, as may happen, a tooth or cog on one of these wheels breaks off, at the point in each revolution at which the gap left by the lost cog meets the other wheel, there is a jar and a noise. We might therefore argue that since loss of a cog is followed by a noise, it was the "normal function" of that cog to prevent or "inhibit" the noise. The cog may then be said to have a dual function: it transmits force and it inhibits noise—and our analogy is well-nigh perfect. Thus, baldly stated, the proposition is manifestly absurd, yet it typifies a line of thought to which the literature of neurology is no stranger.

It is clear, then, that such movements as we may observe after some component of the motor taxis of the organism is out of action, are the resultant, the sum, of the combined activity of the components that remain intact. For example, cerebellar ataxy is that disorder of willed movement that ensues upon a falling out of the cerebellar component and it expresses the activity of what is left of the neural mechanism—it is the product of the attempt at compensation for the lost component. This notion implies, in turn, that the intact mechanisms are themselves modified in their activity under these abnormal circumstances, and thus a fresh

complicating factor is introduced in the attempt to infer the nature of cerebellar function from the observation of what is called, somewhat misleadingly, cerebellar ataxy.

It is this same order of complexity that must invest the attempt to deduce pyramidal functions from the observation of such willed movements as remain after pyramidal activity has been lost. It is many years since von Monakow (1917) emphasized the difficulty of "localizing function" from the study of the symptoms of lesions, and recently, Lashley (1937) has made it clear that this involves the use of intellectual processes somewhat more recondite than those commonly thought sufficient to the task.

My second general point is this, that we shall do well to consider something of the circumstances in which the pyramidal system has evolved. I do not intend to embark upon an erudite phylogenetic or evolutionary study, but I believe that we may hope to get a lead as to the essential quality of pyramidal function by considering the place this system occupies in the human brain as evolved.

Seeking for some way out of that state of muddled suspense that is the first stage of thought upon any unresolved problem, I turned, as I have always turned, to Sherrington's "Integrative Action of the Nervous System," to find, as I have often found, what seems to me the point of view essential to the right approach.

In the illuminating ninth chapter of that magnificent book, entitled "The Physiological Position and Dominance of the Brain," there lie implicit, when not indeed explicit, the clues to the solution of many current problems of neurophysiology.

There we have presented to us a conception of the nervous system in which the entire edifice is reared upon two neurones, the afferent root cell and the efferent root cell. The two form the pillars of the fundamental reflex arc, and on the junction between them are superposed, mediately or immediately, all the other neural arcs, even those of the cerebral cortex itself.

It is the receptor neurone which is the driving force, and in particular the distance receptors that are the great "initiators of reaction." It is round the central endings of their afferent pathways that the cerebral cortex has been elaborated, and it is characteristic of the distance receptors that they tend to treat the musculature as a whole, and to engage it in long sequences of movement that are anticipatory of, and lead up to, later and consummatory events. In this task, the distance receptors have extensive internuncial paths, paths common to arcs that have arisen in-

directly from receptors of various kinds. *The pyramidal tract is, on the efferent side, the principal path of this order, reaching its greatest importance in man.*

Thus we come to the idea of the pyramidal system as the path by way of which the receptors, in particular the distance receptors, can activate and direct movement. It is this notion of directing of movement that seems to me so essential to an appreciation of the role of the pyramidal system, and I cannot do better than to quote what Sherrington says in this matter: thus, "the series of actions of which the distance receptors initiate the earlier steps form series much longer than those initiated by the nonprojicient. Their stages, moreover, continue to be guided by the projicient organs for a longer period between initiation and consummation. Thus in a positive phototropic reaction the eye continues to be the starting place of the excitation, and in many cases guides change in the direction not only of the eyeball but of the whole animal in locomotion. . . . The mere length of their steps and the vicissitudes of relation between bodies in motion reacting on one another at a distance conspire to give to these precurrent reflexes a multiformity and a complexity unparalleled by the reflexes from the nonprojicient receptors." Later, he says, "locomotive progression and distance receptivity are two phenomena so fundamentally correlated that the physiology of neither can be comprehended without recognition of the correlation of the two."

Very recently the same theme has been taken up by Adrian (1947) in his Hughlings Jackson lecture, where he observes that "purposive acts, therefore, must be moulded like the movements of walking, by the controlling afferent patterns which are set up as the act progresses."

The words I wish especially to draw attention to here are the final ones, "set up as the act progresses."

Bartlett, also, in his recent Oliver-Sharpey Lectures on the measurement of human skill (1947) emphasizes the same point, saying "graded action, however simple it may be, has at least one of the fundamental marks of skill—an effector response is not merely set off by a receptor function but is guided and determined by it. The receptor functions that are important in the case of skilled behaviour . . . are always of that kind which claims to register something that is going on in the outside world. So they come to be particularly identified with the operations of the special senses, and especially of those distance receptors which are the basis of tremendous development of the central nervous system. Skill, then, whether bodily or mental, has from the beginning this character of being in touch with demands which come from the outside world."

The pyramidal system is the one through which this guidance is exercised, not in any capacity of initiator but in that of an internuncial path.

Germane to this view of pyramidal function are the many experiments that have shown how the cutting off of afferent impulses from the receptors profoundly reduces the spontaneous activity of the animal. Mettler (1935) and his co-workers found that the decorticated dog seemed unable to initiate movement or to cease a movement once initiated, and they conclude that this initiating function is mediated by the pyramidal system. Bard and Rioch (1937) found the same lack of spontaneity in the decorticate cat, a lack in direct proportion to the loss of afferent pathways to the cortex. Other examples could be cited from the abundant literature on the subject.

We may therefore conclude that receptor activity, including both distance reception and proprioception, is so essentially correlated with pyramidal function that the physiology of the latter cannot be comprehended apart from the recognition of this correlation.

In all these circumstances, it is, I submit, a fair criticism of much modern thought upon the excitable motor cortex and the pyramidal tract, based upon methods of stimulation, ablation and section, that it has considered both in so complete an isolation from the rest of the nervous system, that the essential importance of the sensory side of that system has been forgotten. Further, this abstraction of the part from the whole tends also to obscure the significance of the part abstracted, and in this instance has led directly to the attribution to the pyramidal system of functions which, as an internuncial system, it could not fulfil. Thus, Tower endows the pyramidal tract with "full responsibility" for the discrete control of movement, and holds that in virtue of its "discriminating qualities" it affords the cerebral cortex its effectiveness as "an agent of choice." Surely, to take this view is to put the cart before the horse.

It is essential, therefore, to stress the importance of the idea of the receptor system as initiating and directing willed movements, in contrast to the widespread assumption that we may usefully contemplate the physiology of movement as starting *ab initio* from a mechanically conceived "keyboard" in the motor cortex. This point of view derives from a still earlier assumption, namely, that we may regard the highly artificial phenomena ensuing upon electrical stimulation of the cortex as reproducing the normal activity of the brain in initiating and directing willed movements, or at least as not differing from this in a degree or manner calling from us for any intellectual exegesis. The willed movement, the "precurrent" reaction as it so commonly is at its start, is not characteristically

predetermined in form, duration or complexity, for it is moulded throughout its course by impulses deriving from the visual, extero- and proprioreceptors. It is thus profoundly unlike the motor response to electrical stimulation of the cortex.

It would seem, therefore, that we may look upon the pyramidal *system as an internuncial, a common, pathway by which the sensory system initiates and continuously directs, in willed movements, the activities of the nervous motor mechanisms.* This sensory afflux is a condition of willed movement, and unless we consider both in association we cannot hope to see the purpose of either.

Having criticized some modern thinking upon pyramidal functions for considering these without due regard for what has been left out of the abstraction, it would ill become me to fall into the same error. This I should be doing were I to make no reference to the psychological considerations involved in the use of the term "willed" as applied to movement, and developed my argument as though willed movements were simply and immediately responses to sensory stimuli. An "educated skill," to use Bartlett's apt expression, is a psychophysical process or event, and between the impact of sensory impulses upon the cerebral sensory mechanisms and the motor reactions lie processes of choice, selection, judgment and timing which, while they have their concomitant physiological processes, belong also to the realm of the mind. There is motor behaviour, too, that, while its performance demands sensory direction, is initiated by no discoverable present sensory stimulus, but derives from mental processes.

It is not a part of this attempted formulation of an hypothesis of pyramidal function that I should even enter this complex and difficult field of discourse. Let it suffice that we recognize that in the definition just given of the role of the pyramidal system there has been omitted from explicit consideration the psychological aspects of what is involved in the term "willed" as applied to movements; that but a fraction of the total problem of movement is being considered; and that we recognize that willed movement is not simply a response to sensory stimuli.

In the light of Sherrington's conception of the pyramidal system, we may now see it in its due relation to the sensory side of the nervous system. We can no longer continue to regard it as something enjoying a most unphysiological autonomy within the nervous system, nor as possessing "discriminating" functions which are the properties of synaptic fields but not of conductors.

(2) Hemiplegia as a Basis for the Study of Pyramidal Function.

The value and the unique quality of hemiplegia in the human subject as the material of study in our present connection can hardly be overestimated. They consist in the infinite gradations of defect of pyramidal function hemiplegia presents to the clinical observer, in the slow recessions and the gradual developments of the state he may observe in his patients, in the stable residual states of all degrees of severity that are available, and finally in the degree of that essential co-operation between subject and observer upon which any refined analysis of willed movements must rest. In all these respects the clinician is more favourably placed than the experimental worker on animals, all of whose lesions are acute, whose ablations and sections are irreversible, and whose subjects cannot really co-operate.[1] I suggest therefore to this audience of clinicians that we are in a unique position to contribute signally to the study of pyramidal function, and to have confidence in our findings as of crucial significance.

(*i*) *The Dual Character of Hemiplegia.*

In considering whether we are to equate hemiplegia, as we encounter it clinically, with pure pyramidal defect, we have to remember that it includes not only loss of willed movements, but also, in most instances, numerous positive or "release" manifestations: namely, increased tendon reflexes, clonus, hypertonus, and upon occasion the tonic neck reflexes of Magnus and de Kleijn (Simons, 1923; Walshe, 1923). When we consider the variability of these components, it is clear that for the clinician hemiplegia is far from being a uniform state. The question arises whether all these phenomena, negative and positive, are the consequences of abrogation of pyramidal action. Is it possible that some at least of the positive symptoms may be due to release of segmental motor mechanisms from the control of some other efferent path descending from the cortex, a path put out of action by the same lesion that has involved the pyramidal system? In other words, are two negative or destroying lesions concerned in the production of the typical residual spastic hemiplegia, one pyramidal the other extrapyramidal.

[1]The experimental production of slowly progressive hemiplegia has not, as far as I am aware, been attempted, but there is a method by which it might possibly be achieved: namely, by implantation in some chosen site in the cerebral hemisphere of an animal, of a small hydatid cyst, which by its growth would reproduce the slowly progressive lesion of human pathology. It is conceivable that by some such means the range of physiological analysis of cerebral function by the experimental method might be extended.

It was long assumed by clinical neurologists that pyramidal defect by itself accounted for all the phenomena of hemiplegia, negative and positive alike, and the dual character of hemiplegia was expressed in the simplest possible form of the familiar Jacksonian doctrine of release of function. Many years ago, however (1919), I suggested that we might have to modify this view, on the basis of certain clinical and experimental findings, and to entertain the possibility that negative lesions of two descending systems might be in question, that loss of movements might ensue from the pyramidal lesion and that some at least of the positive symptoms might express release of subordinate motor mechanisms from a second descending pathway and neuronal system.[1] By clinico-pathological study it has never been possible to resolve this uncertainty, for disease and injury in man do not provide us with clean sections of the medullary pyramids, and we have to allow that in all lesions producing spastic paralysis, whether hemiplegia or paraplegia, it is possible that extrapyramidal as well as pyramidal fibres may be involved.

Further, clinical study has taught us (i) that there is in hemiplegia no constant direct relation between the severity of loss of willed movements and the degree of hypertonus present, (ii) that we frequently encounter marked increase of tendon-jerks where there is no unequivocal increase of tone, (iii) that associated movements (tonic reactions) are not seen save in the presence of marked hypertonus, and Magnus and de Kleijn tonic neck reflexes are not constantly, or even commonly, found, even in the presence of such a degree of hyptertonus. That these components should show such variable relations to one another does point to the operation of more than a single factor in the production of the familiar picture of spastic residual hemiplegia, and thus far does support the speculation expressed by me in 1919.

We must turn, therefore, if we are to resolve this uncertainty, to those cases of experimentally caused hemiplegia in which the lesion is section of the medullary pyramid in cat, dog and monkey (Tower, 1935, 1940, 1944; Marshall, 1934; Ranson, 1936; Liddell and Phillips, 1944). In cat

[1]From what has been said earlier of the possible difference in constitution of the pyramidal system above and below the level of the medullary pyramid, and also because "extrapyramidal" efferent fibres of motor function arise within the limits of the excitable motor cortex, it is clear that we cannot equate a lesion of the motor cortex with one of the pyramidal tract at or below the level of the medullary pyramid. Thus, three elements may be involved in a destroying lesion of the motor pathways between the pre-Rolandic cortex and the medullary pyramid: namely, direct corticospinal fibres, collaterals given off by corticospinal fibres, and extrapyramidal efferent fibres of cortical origin.

and dog there is some degree of increased tone of extensor incidence in the limb muscles. Tower describes this as "stiffness" but provides an argument, not easy to follow, for regarding this stiffness as being merely an absence of flexor activity: thus preserving her thesis that the picture of pyramidal lesion in the cat is a purely negative one. However, Marshall, Ranson, and Liddell and Phillips all agree that hypertonus is a constant feature of pure pyramidal section in cat and dog.

In answer to the question "Is the syndrome of pyramidal defect one of purely negative character without any release phenomena in the case of monkey and chimpanzee?" Tower replies with a categorical affirmative. "In the realm of motor function," she reports, "the condition is unquestionably one of deficient function, without phenomena of release," and putting the matter conversely, says, "there is no evidence of inhibitory function" of the pyramidal system.

As in the case of her study of the cat, however, this conclusion is not quite in accordance with the facts she describes, for she records a proprioceptive grasp reflex in both monkey and chimpanzee ("emphatic" in the latter) and a Babinski plantar response in the chimpanzee.

Now if, as is generally agreed, we regard the tonic grasp reflex as a proprioceptive reaction (Walshe and Robertson, 1933; Walshe and Hunt, 1936), and the Babinski plantar response as an integral part of a phasic nociceptive flexion reflex (Walshe, 1915), then we have as a sequel to a pure destroying lesion of the pyramidal system in these animals release manifestations in both the tonic and the phasic fields of motor reaction. Further, Tower reports that in the hypotonic musculature of the hemiplegic monkey, tone is influenced by posture, and is increased in the antigravity muscles when the animal is standing. How this variation is to be accounted for if not by tonic reflexes of the order described by Magnus and de Kleijn is not clear, and these must surely be release phenomena.

It is surprising in these circumstances to find Denny-Brown (1945) observing that "the final blow to the clinical conception of disorder of the 'pyramidal system' was delivered by Sarah Tower in her classic description of the monkey after section of the pyramid in the medulla."

Plainly the obituary is premature, for the evidence remains in favour of a dual symptomatology in hemiplegia due to pure pyramidal lesion, though it does not exclude the possibility that *some part* of the positive manifestations may be due to release from the control of extrapyramidal systems of cortical origin. Further, the view that the pyramidal system has no function of control or inhibition makes it difficult to understand how it can play the very complex role imputed to it. Lloyd (1941) has

provided direct evidence of reciprocal innervation (excitation and inhibition) of internuncial neurones in the grey matter of the spinal cord by impulses descending the pyramidal tract. Denny-Brown (loc. cit.), also, paradoxically enough, has given cogent reasons in favour of the exercise of such functions by the pyramidal system, and to these we shall later return.

(*ii*) *The Loss of Willed Movements in Hemiplegia.*

Our purpose being to consider the role of the pyramidal system in the innervation of willed movements, we may leave the question of the positive or release symptoms which we must, however, still regard as an essential item in the total picture of loss of pyramidal function.

(*a*) *Pyramidal Lesion in Monkey and Chimpanzee*

It would take us too far afield to describe the various states of loss of movement resulting from pyramidal lesion throughout the wide range of animals from cat to anthropoid, and I propose, therefore, to concentrate upon Tower's (1940, 1944) account of the loss of movement seen in monkey and chimpanzee after section of the medullary pyramid. No available account compares with this in detail and completeness, or in the precision with which the lesion was produced and anatomically controlled. Subsequently, I shall seek to elicit from the disturbances of the upper limb in clinically observed hemiplegia, some of the principles illustrated by pyramidal defect in man.

I confess to a difficulty in summarizing the facts of observation recorded by Tower, because she has embodied her account in a terminology that presupposes the theoretical conclusions she proceeds to draw, and fact and hypothesis are thus not always easy to differentiate. This gives in places an appearance of inconsistency in the description. Thus she finds that there is diminished general usage and loss of initiative in all the limb movements, and such movements as are retained are weak and often tremulous, inaccurate, incapable of modification while in progress, call for prodigious effort and lead to excessive fatigue. It would appear, therefore, that there is no order or aspect of willed movement that is not gravely impaired. In addition, hopping and placing reactions of the lower limbs are abolished. However, this gross affection of willed movements is selective, for while digital movements are totally abolished, movements leading to assumption and maintenance of postures, reaching and grasping movements persist. They are even said to "function well," but in what sense is not clear in view of what has already been said of their state of efficiency. Nevertheless, an antithesis begins to be developed

between these two categories of movement, the former being "sharply discriminated against" by pyramidal lesion and "selectively destroyed." In the plain terms of description as given by Tower, this antithesis is not so readily apparent. Yet it is further developed in the final formulation of pyramidal function, and comes to dominate the hypothesis ultimately propounded. Thus, the unique role of the pyramidal system is the initiation and control of discrete movements, especially those of the digits. Secondly, it "enters into all somatic motor activity of any complexity to confer upon the stereotyped extrapyramidal performances adjustability in space, modifiability in the course of execution, and all modulations of pattern which make for aim, accuracy, economy, liability and finish" (1940, p. 87). Thirdly, by its tonic function it provides for smooth and continuous action. Fourthly, it shows no sign of inhibitory activity.

Willed movements are thus deemed to fall naturally into two categories, in respect both of their characters and of their anatomical substrata. There is a category of "discrete" movements pyramidally initiated and controlled, and one of "stereotyped" movements extrapyramidally initiated and controlled. Not only is this second category "stereotyped," but it lacks qualities of adjustability, modifiability, accuracy, aim, lability and finish. These qualities, in the normal motions of the intact animal, are "conferred" upon it by the "modulating" action of the pyramidal system. It is important, if we are to understand the essential nature of Tower's hypothesis, to bear this curious relationship of pyramidal to extrapyramidal components in willed movement in mind.

In a recent paper (Walshe, 1947) I have discussed the ambiguous nature and usage of the terms "discrete" and "stereotyped," and the fact that once these are given definition they are found unsuitable to any classification of willed movements and do not provide a true antithesis.

What is more important is that we have here a conception of central nervous activity that it is difficult to accept. The attachment of the two hypothetical categories of movement, discrete and stereotyped, to separate anatomical structures, the pyramidal and extrapyramidal systems respectively, necessarily involves certain corollaries. *Ex hypothesi*, extrapyramidal components of willed movements lack aim, accuracy, &c., and thus we find ourselves once more with a "protopathic nervous system" in replica, with its own peculiar physiological properties and shortcomings and its own distinct anatomical substratum, the extrapyramidal system. Set over it we have the pyramidal system which has not only its own specific function of initiating "discrete" movements, but a secondary function of conferring upon the crude activities of the extrapyramidal system

those high-grade qualities it lacks. For "pyramidal" write "epicritic" and the analogy with Head's conception of the afferent nervous system is complete.

Now it is surely not to be disputed that pyramidal and extrapyramidal systems are both in action in, and are essential to, all possible willed movements, but their respective roles cannot be generalized within the limits of this physiologically unreal scheme which pictures a type of nervous system that nature has never presented to our gaze (cf. Walshe, 1942*a*).

It is difficult to believe in an extrapyramidal motor system so evolved that, left to itself, it functions without economy, accuracy, aim or finish. On the contrary, we know that when acting in reflex fashion the complex arcs of cord and brain-stem do not so behave, but show a beautiful precision and adaptation. It is their nature to do so, nor in these circumstances do they owe anything to the activity of the pyramidal system. Further, there are various features of pyramidal deficit that do not tally with the hypothesis. Thus, hopping and placing reactions are surely not discrete, and they form a stereotyped pattern. Yet they are completely abolished by pyramidal section.

(*b*) *Defect and Loss of Willed Movements in Clinically Observed Hemiplegia.*

Compared with the relative uniformity of its experimentally produced counterpart, hemiplegia as seen in the human subject is a thing of almost infinite variety within the wide range of its extreme manifestations, and it presents unique opportunities for the observation of the evolution and dissolution of motor function as we study recovering or developing hemiplegias and all grades of stable residual weakness. To be familiar with all this is indeed to have a liberal education in clinical neurology.

To seek to describe or even to enumerate all the defects of movement to be seen in these circumstances would be a task beyond the scope of the present occasion. I believe it unnecessary for me even to attempt it, because the general features of the loss of movements characteristic of hemiplegia are sufficiently revealed by a study of the hand and arm, in a subacutely or slowly developing hemiplegia.

In the upper limb, the paresis first appears in the movements of the hand and digits, and then spreads to involve the limb in a central direction and in that "compound order" of paralysis long ago described by Jackson, and familiar to every neurologist.

Three features are to be noted in this process: the number of movements normally possible is progressively lessened, and this involves a

marked diminution of the variety of possible movements because many of these are combinations and sequences of smaller movements. Thus compound movements of the hand and digits weaken, dwindle and disappear early. Secondly, all movements become markedly slow in initiation and performance, and thirdly, such capacity as is normally possessed to move digits individually lessens progressively. The progressive diminution of the number of possible movements necessarily leads to a greater uniformity of pattern of hand movements, and this we might speak of as an approach to stereotypy in the hand's activities, but this, be it noted, is a very different thing from the statement that discrete and variable movements disappear and leave a separate category of stereotyped movements; such a summary would be a travesty of what is actually happening.

In view of what has been said earlier of the existence of a specific category of discrete movements, it is necessary to be explicit as to what may be seen as the hand weakens with the development of hemiplegia. Few, if any, of us possess the power to move one digit only at a time. Even in the familiar gesture of beckoning, the appearance of discreteness is illusory, for we normally fix the other digits by firmly flexing them into the palm and then closing the flexed and opposed thumb over them. Even so, the thumb and digits can be felt to contract concurrently with the index, and if we try to beckon with the index while the thumb and other digits are open, we see them all enter into the movement and we are wholly unable to inhibit their participation. Even the simple movement of alternate flexion and extension of a digit is always accompanied by a similar movement of lesser range by its fellows. In short, a discrete movement of a single digit is a feat none of us is capable of. What happens as hemiparesis develops is that we become *less able* to move the digits differentially, but the change is one of degree and not one of kind.

Undoubtedly the first group of movements to disappear are those in which the interossei, lumbricales and the flexors and opposers of the thumb engage. Abduction of the fingers and extension of the phalanges are earlier and more severely affected than adduction. As this occurs, the combinations of flexion, extension, adduction and abduction are lost and the hand is at once severely disabled, for these are the movements that give the hand as a whole its wide range of rapid movements. This is easily seen by the simple test of asking the patient to touch each finger tip in succession to the tip of the thumb, beginning either with index or with little finger. There is a stage at which while the necessary flexion of each digit remains, the necessary adduction and opposition are lost and the thumb and finger tips are not approximated, but flex futilely into the palm.

In short, the hand and digits and after them the forearm, arm and limb girdle are progressively denuded of movements, and with this impoverishment, the range and variety of mobility necessarily lessens, for the elements out of which the normal combinations and sequences of movement consist are not there.

Thus it is that the wider and the more complex the combinations and sequences that go to make up a given willed act, the more gravely its execution is impaired. Further, since from its very structure the hand is capable of a wider range of different movements than are possible in the proximal segments of the limb, it is the hand that exhibits most profoundly the consequences of defect in pyramidal function.

An equally striking feature of the situation we are considering is the very marked delay in starting and the slowness in performing the movements that remain possible in the affected hand and arm. In his famous Bridgewater Treatise (1829) on "The Hand, its mechanism and vital endowments," Sir Charles Bell discusses the relations of power and velocity of movement in muscles, pointing out that the small hand muscles are characterized in action by their velocity rather than by their power, the proximal muscles by their power rather than by velocity of contraction. He says "the same interchange of power for velocity, which takes place in the arm, adapts a man's hand and fingers to a thousand arts, requiring quick or lively movements . . . these small muscles (Interossei and Lumbricales) attached to the near extremities of the bones of the fingers where they form the first joint, being inserted near the centre of motion move the ends of the fingers with great velocity. They are the organs which give the hand the power of spinning, weaving, engraving; and as they produce the quick motions of the musician's fingers they are called by the anatomists *fidicinales*."

Although, therefore, in the paretic arm the movements that are left are naturally the slowest, there is undoubtedly a marked slowing down even of finger movements when any remain, and this is associated with every evidence of great effort on the part of the subject and of rapid fatigue when such weak slow movements are persisted in.

This brief sketch of the sequence of events when loss of pyramidal function evolves slowly in a part particularly under its influence may be resolved into certain elements: (i) There is a slowly progressive waning and disappearance of movements, beginning in hand and digits and spreading proximally up the limb in a central direction and in compound order. Ultimately, there may be no movements that are not lost, but there is an intermediate stage at which some movements of every part of the limb

are lost. As the number of retained movements dwindles, the motions of the limb as a whole, or of the hand considered separately, tend to become more uniform, until with profound reduction so few movements are left that the *patterns of movement* left qualify for the term "stereotyped." However, this is not because a specific category of stereotyped movements is left uncovered in its native imperfections by the loss of a different category of "discrete usage," but simply because when only one or two movements remain there can be no variety. (ii) From the structural qualities of the hand it possesses a greater number and variety of movements, and of quicker movements, than the proximal parts of the limb, and in the characteristic evolution of paralysis, the movements of the leading part, the hand and fingers, suffer first and most severely. (iii) There is great and increasing slowness of movements.

I do not find it possible to generalize this state of affairs in terms of a differential effect upon two distinguishable categories of observed movement, discrete and stereotyped, the one being lost and the other intact but lacking refinement by the category lost. Not only is there a loss of relatively simple movements which is maximal at the distal part of the limb, but there is strikingly a loss also of those long complex movement sequences; of those precurrent or anticipatory motions, that employ the musculature of the limb as a whole; that is, in the fashion in which it is normally employed in willed motion. Initiation and direction of movement are both impaired or lost because the internuncial path by which travel the impulses that should mediate these functions is interrupted. Sensory impulses reach the cortex and are therein integrated and their psychical concomitants in consciousness are intact, but *the way out* for the activating and directing impulses from motor cortex to subordinate motor centres and ultimately to the final common path is blocked. Every form of willed movement suffers accordingly.

(3) The Role of the Pyramidal System in Willed Movements.

The inference with which we started, one taken from Sherrington's "Integrative Action," is that we should regard the pyramidal system as an internuncial one, a sort of common path standing between the receptors, the distance receptors being dominant, and the motor mechanisms of the nervous system. The distance receptors are the great initiators and directors of all those sequences of willed movement, simple and complex, short and long, anticipatory and consummatory, that compose the willed mobility of the intact individual.

This mobility involves what Jackson spoke of as co-ordination in space

and co-ordination in time, and for purposes of analysis it is necessary to think of these two aspects of a single function in separation, remembering always that they are not separated in action. Jackson's aphorism in which he speaks of the two as, respectively, the harmony and the melody of movement aptly expresses the relation and the natural unity of the two.[1]

Now co-ordination in time; that is, the ordered sequence of movements, must surely be intimately dependent upon sensory direction, while co-ordination in space, that is, the composition of movement at any given moment, has to be thought of as closely dependent also upon the patterns of movement laid down in the cortex.

This point of view reveals another aspect of our problem, namely, whether it is an adequate conception of pyramidal function to think of the system as simply internuncial. Does it not, must it not, play some more complex role in co-ordination in space than this view allows? This in turn raises the larger question of the role of the pyramidal system within that physiological entity we speak of as the motor cortex, and to this we must now give some attention.

(i) The Relation of Pyramidal System to Motor Cortex.

The controversies and the wide differences of opinion as to the role and constitution of the motor cortex which have characterized the relevant literature during recent years (cf. Walshe, 1942*b*) depend upon something more fundamental than differences about the meaning of words, though these have played a large part, and they indicate a general failure since the time of Jackson to grasp all the implications of the cortical control of movement. For example, what is the relation between the motor cortex and that forward lying cortical region whose functions we may speak of as eupraxic, that is, what is the relation between Jackson's middle and highest levels? What is the precise role of the pyramidal system of neurones within the motor cortex, and are they right who assume, as some appear to do, that the cells of origin of the pyramidal tract constitute the entire motor cortex?

For some years an influential body of opinion has equated the cells of origin of the pyramidal system with the motor cortex, and has further restricted this by assuming that only the so-called "giant cells" of Betz give rise to pyramidal fibres. Though this hypothesis has not been explicitly

[1]In a very suggestive article, Lashley (1937) has given reasons for thinking that co-ordination in time and co-ordination in space represent different types of integration, calling for different mechanisms of organization in the cerebral cortex, and thus for spatial separation of the fields in which the different processes operate.

disavowed by its proponents, it is not likely that they would now seek to sustain it. Nevertheless, hypotheses of this order become fixed in the relevant literature and continue to influence thought long after they are found to be inadequate. It is clear therefore that as long as we continue to regard the giant cells as the sole cells of origin of the pyramidal tract, and equate them with a "histologically defined" motor cortex (Fulton, 1933), we cannot possibly begin to think of the pyramidal system as simply an internuncial one.

But the facts require that, and the time has come when, we must abandon this point of view with the anatomical fallacies upon which it was based, and seek some wider generalization of the role and constitution of the motor cortex and of the pyramidal system. While the latter is plainly the main projection path of the former, I submit that we err when we assume that the cells of origin of the pyramidal tract, however widely we now know them to be distributed, make up the motor cortex *in toto*. Yet implicitly, when not explicitly, this is in fact what we have commonly assumed.

It is not within the scope of my present limited task to generalize the entire motor functions of the frontal cortex, but the main outlines of what, following Hughlings Jackson, I conceive these functions to be will serve to orientate my hypothesis of pyramidal system functions.

It is clear that however widely Jackson's views on the organization of the excitable motor cortex, his "middle level," may have influenced neurological thought in our time, his conception of the "highest level" of motor integration has not influenced it at all. Thus, the final representation of "educated skills," the function of eupraxia as it may be called, is on Jackson's hypothesis laid down in the frontal cortex anterior to the excitable motor cortex. Yet, for many years, following Liepmann's famous exposition we have thought of apraxia, that is, of disorders of eupraxia, as solely associated with lesions of the supramarginal gyrus—though Liepmann was never so exclusive—and we have been content with more or less conventional classifications of apraxia: e.g. ideational, motor, &c. These disturbances are now indeed commonly spoken of as indicative of a lesion of the supramarginal gyrus, or of subcortical paths leading from it to the precentral gyrus and via the corpus callosum to the crossed precentral cortex. Yet, with some inconsequence, we continue to regard motor or expressive aphasia and agraphia as forms of apraxia involving articulate and written speech and to localize the specific losses of these skills in lesions of the frontal cortex. It may be questioned whether lesions of the supramarginal gyrus and of paths leading from it ever yield the isolated loss of some

specific "educated skill" such as we see in expressive aphasia, other skills being left intact, and it is clear that there are problems involved in this question of the highest level of physiological integration of movement that have scarcely yet been recognized. But it is not my task to discuss this subject further now, and the proposition I submit is that whatever disorders of eupraxia may ensue upon lesions of the parietal cortex, there is in fact a representation of educated skills in the frontal cortex, a representation which constitutes Jackson's "highest level."[1] The functions of this are not to be conceived as of the mere building up *ad hoc* of learned movement-complexes, from elementary units of movement represented in the precentral gyrus. Its role is that of a true representation of those large and infinitely complex movements that, following Bartlett, we can speak of as educated skills, and since these of their nature involve long sequences of movement, it may well be, as Lashley (loc. cit.) has suggested, that temporal co-ordination, co-ordination in time, is the essential integrative mechanism subserved by this level. To seek to name in morphological terminology the precise topography of this representation within the frontal cortex would be to pretend to that figmental precision that is the major and vitiating error of modern cortical cytoarchitectonics (cf. Lashley and Clark, 1946).

A destroying lesion of this anatomical substratum of the eupraxic mechanism abolishes the willed initiation and performance of one or more "skills," while leaving unimpaired the willed performance of other skills even though these may employ some or all of the muscles engaged in the now lost skills. The abolition of such a skill, which may range in complexity from articulate speech to the appropriate handling of some familiar tool, we speak of as "motor apraxia."

It is of course probable that there are many as yet unidentified expressions of negative lesions of the frontal eupraxic mechanism: for example, the striking general immobility and lack of initiative of some cases of frontal lobe neoplasm may be a generalized highest level paralysis of almost all skilled usages of the musculature, for this level does tend to engage the musculature as a whole.

More familiar to us are the effects of destroying lesions of the middle level, the motor cortex. Here also movements are lost while other movements employing some or all of the muscles engaged in the lost movements remain intact. The movements lost are of a simpler order than

[1]There is some experimental evidence suggesting that a motor apraxia ensues in the monkey upon ablation of the so-called "premotor" cortex (cf. Jacobsen, 1932, *Proc. Assn. Res. Nerv. and Ment. Dis.*, **13**, 225).

the "educated skills" we have been considering. The latter also, however, must suffer disorder from a middle level lesion because this level and its projection path link the eupraxic mechanism mediately with the musculature, but this disorder is not a specific paralysis of a skill such as characterizes a highest level lesion. In neither case, be it noted, can we rightly speak of a paralysis of muscles: a point to which we will return later.

We have, therefore, in these two physiological levels two orders of representation, both necessarily employing the pyramidal system; the highest level mediately, the middle level immediately. The sensory afflux we may regard as acting immediately upon the highest level, and only indirectly and through this upon the middle level.

Experimental evidence suggests that the electrical excitability of the motor cortex depends upon cells that lie in the same fifth cortical layer wherein the cells of origin of the pyramidal tract are to be found, but this does not allow us to equate the motor cortex with these cells, and I submit that they are in all probability simply that part of the motor cortex considered as a physiological unit which constitutes the "way out," and that, in their larger relations, they form with their axones that internuncial system Sherrington originally designated them.

(*ii*) *The Relation of Pyramidal System to Subordinate Motor Mechanisms.*

We return, then, to our first conception of the pyramidal system as an internuncial one employed by the receptor system in the activation and direction of willed movements. A great deal is now known of the motor mechanisms which, through the medium of the pyramidal system, the receptors activate and control. The work of Magnus and his school, building upon foundations so securely laid by Sherrington, has revealed what the neuraxis is capable of in co-ordination of movements and of postures, and we know something, too, though not yet all, of the role of the neocerebellum—an organ that is essential to the perfect activation of the segmental motor machine in willed movements (Walshe, 1927).

Comparative physiology has also taught us how, as the animal phylum is ascended, the segmental machine becomes more and more dependent upon activation from the cerebral cortex and the profoundly immobile, helpless state of the monkey after bilateral pyramidal section reveals the measure of this dependence.

So far nothing has been said of the "how" of this activation and direction. The notion of control of lower levels by higher is fundamental in the Jacksonian conception of evolution in the nervous system, and control necessarily involves inhibition as well as excitation. Yet Tower has pre-

sented us with an hypothesis of pyramidal activity in which inhibition is excluded. Since she speaks (1936) of "fractionation" of complex synergies as a primary pyramidal function it is difficult to see how inhibition can be excluded from the operative processes concerned.

Denny-Brown (loc. cit.) has recently drawn attention to some observations of Coghill that are germane to the subject, showing how the development of segmental or local reactions may be arrived at by the fractionation of earlier developed general patterns. Such a mode of evolution of function involves inhibition as a prime factor. It involves the isolation of a movement by the inhibition of the other elements in the original pattern: a "differentiation by exclusion" as Denny-Brown expresses it, adding that "a cortical movement in such a conception would require a widespread inhibitory counterpart over all other postural or progressive reaction except that which aids and augments the action desired."

However, when we recall the infinite complexity of willed movement patterns, it seems unlikely that differentiation by fractionation can by itself be adequate. At most it can be little more than a necessary preliminary to differentiation by combination (spatial and temporal), and this notion brings us near Leyton and Sherrington's classic interpretation of the functions of the excitable motor cortex. What I am proposing is the idea of the cerebral cortex, sensory, eupraxic and motor, the seat of a constantly changing flux of excitation patterns, using the pyramidal system as the pathway by means of which it achieves a fractionation and combination (in time and in space), by processes of selective inhibition and excitation of bulbospinal motor mechanisms, of those reflex synergies that the experimental study of the variously truncated nervous system has revealed to us in such abundance. By this process of fractionation and combination there is woven the complex and constantly varying patterns of willed movement.

In acting as the agent of this process the pyramidal system is passive in the sense that it is driven by the receptors through the cortex. This process of driving is what Bartlett (loc. cit.) expresses as the "simple and basic fact of detailed determination by receptor function"; a function which involves the integration of all sensory sources and provides the basis of spatial and temporal co-ordination, whether of large movements or of small.

But no hypothesis can leave out of account the role of basal ganglia and cerebellum in the formation of willed movements. It is specifically in relation to willed movements that the neo-cerebellum acts, for the reflex reactions of the thalamus animal are not impaired by ablation of the cere-

bellum, and cerebellar ataxy is essentially a disorder of willed movements (Walshe, 1927). Nevertheless, precisely how cerebellum and pyramidal system collaborate remains unknown. In a still deeper obscurity lies the role of the basal ganglia. No specific contribution to willed movement, or even to the complex reflex reactions of the neuraxis, has so far been conclusively apportioned to them. In the circumstances, speculations abound, but as they add nothing to our knowledge of pyramidal function it is not relevant to discuss them. Therefore, any present attempt at a comprehensive view of the functional relations of the pyramidal system must suffer from gaps in our knowledge, the importance of which it is difficult to assess.

It is now possible to correlate in broad terms the results of a destroying lesion of the pyramidal system with the views of the functions of this system which have been sketched. It is reasonable to expect that willed movements will fail in proportion as the activating influence of the receptors, the distance receptors in particular, upon the motor mechanisms fails to reach these through the pyramidal tract. The failure will be selective where pyramidal activity is impaired rather than wholly lost, involving most severely the most complex and long lasting movements which are most dependent upon continuous sensory guidance. These will be movements of what Jackson spoke of as the leading parts. Thus, the arm and hand, that "delicate explorer of space in manifold directions," may be expected to show a greater disablement of its activities than the lower limb with its far more limited repertoire of movements, and their more deeply impressed organization in the motor centres.

This selectivity we should expect to find one of degree rather than one of kind, governed rather by considerations of complexity than of mere size of movements.

Further, with impaired direction, such movement sequences as persist will not vary during execution to adjust to what Sherrington speaks of as "the vicissitudes of relation between bodies in motion reacting on one another at a distance."

All these defects are, indeed, what we have found to be characteristic of the paralysis following pyramidal lesion.

(iii) The Relation of Pyramidal System to Musculature.

Finally, one more point calls for mention in any discussion of pyramidal function. The pyramidal tract is the projection path of the motor cortex, and we know that there are two views of the physiological organization of the latter: the generally accepted view that the representation

is one of movements, and the newer view of Foerster (1931), Fulton (1936), and Hines (1944), that the representation is one of single muscles.[1] If we accept the latter view we should surely have to hold also that the pyramidal tract innervates muscles as such, and that pyramidal defect must show itself as a paralysis of muscles rather than of movements. Indeed, Foerster has not hesitated to commit himself to the statement that he has seen an isolated paralysis of a single muscle from a cortical lesion. No other clinician, I think, has ever made such a claim, which, as every student of Beevor's exhaustive studies on this subject knows, is directly opposed to all clinical experience. Finally, also, Lloyd's (1941) account of the spinal mechanism of the pyramidal system in cats affords no support to any hypothesis of a direct innervation of "single muscles" by this system, but does provide evidence incompatible with it.

In conclusion, as I realize full well, this paper is no more than an adumbration, a sketch, of a theory of pyramidal functions expressing a point of view for which the most I claim is that it is an attempt to go back forty years to the philosophical principles enunciated in Sherrington's "Integrative Action" and to those, still more remote, enunciated by Jackson; principles somewhat lost sight of in the years that have followed. It is also a point of view that, I believe, contains nothing contrary to the known principles of neural function, and one which does not involve that intolerant use of abstractions which has tended to obscure the great merits of Sarah Tower's exhaustive study of pyramidal lesion in monkey and chimpanzee; a study which, when reinterpreted, must prove of high value in the solution of the difficult problems of pyramidal function.

(4) Summary.

The pyramidal tract is an internuncial path, a common path, standing between the massed receptors on the one hand and the motor mechanisms of the nervous system on the other. It has evolved in particular relation to the development of the distance receptors, perhaps vision alone, and has

[1]Professor Henry Cohen has pointed out to me in a private communication that "it is philosophically indefensible to base an hypothesis of a physiological organization of the cerebral motor cortex upon the morphologist's arbitrary nomenclature of so-called 'single muscles.' To do so is comparable with the attempt to interpret geological formations in terms of the arbitrary delimitations of country boundaries." Indeed, the morphologist's "single muscle" is only fortuitously, when at all, a physiological unit, and it does not appear that the proponents of the theory of a representation of "single muscles" in the cortex have ever asked themselves to what precisely they refer when they use this term.

reached its highest importance in man. It is the path by way of which the distance receptors put the motor mechanisms of the nervous system in operation; activate, and thereafter direct their action throughout the performance of those sequences of willed movement, short and long, simple and complex, characteristic of the normal organism. *The pyramidal system of itself initiates nothing, and to speak of it as "responsible for" this or that category of movements is to ignore the source and motive power of its activities. It is simply the channel through which pass the impulse volleys by which willed movement is activated and continuously moulded by controlling cortical afferent patterns of excitation.* If this be so, then it is concerned with all possible willed movements, and all aspects of willed movement, and if, as has been postulated, the cortex by way of the pyramidal system fractionates and then combines the functional elements of reflex segmental mechanisms, then every willed movement, short and long, small and large, restricted and ample, is as wholly pyramidal as it is extrapyramidal, and separate categories of movement thus anatomically classified or grouped as discrete or stereotyped have no existence as phenomena; they are abstractions not discernible as things or events in nature.

The conception of pyramidal function now so widely current has three grave defects: it overlooks the simple and basic fact of detailed determination by receptor function, and treats the sensory system as irrelevant; it fails to appreciate that the distance receptors, of which the pyramidal system is the agent, tend characteristically to employ the musculature as a whole rather than in anything that can accurately be called discrete movements; and thirdly by implying an equation between the cerebral motor cortex and the cells of origin of the pyramidal tract, it is forced to attribute to the pyramidal system functions far beyond those of its real role as an internuncial path.

Precisely how the pyramidal system, or rather the cerebral motor cortex, and the neocerebellum are related remains obscure, but that the activity of the latter is essential to the co-ordination of willed movements, and that this is its main function, is clear.

Finally, a neurone system fulfilling the role here attributed to the pyramidal system must surely be the medium of inhibition as one mode of control of subordinate motor mechanisms. If this be so, then a corollary of loss of pyramidal action is a dual picture with positive and negative elements. In fact, in both the phasic and tonic fields of motor reaction there is clear evidence of positive or release symptoms. It seems certain, for example, that the spinal flexion reflex, of which the Babinski plantar response is an integral part, is to be so regarded, while in the tonic field

indications are not lacking that here also release of function is part of the picture of pyramidal defect.

I cannot conclude these observations without expressing my grateful thanks to Dr. Gordon Holmes for the stimulating and critical comments I received from him during the writing of this paper.

REFERENCES.

ADRIAN, E. D. (1947), *Brain*, **70**, 1.
BARD, P., and RIOCH, D. M. (1937), *Bull. Johns Hopk. Hosp.*, **60**, 73.
BARTLETT, F. C. (1947), *Brit. Med. J.*, i, 835.
BELL, CHARLES (1829), The Hand, its Mechanism and Endowments, London.
DENNY-BROWN, D. (1945), Diseases of the Basal Ganglia and Subthalamic Nuclei, Oxford Loose Leaf Medicine, N.Y., Vol. VI.
FOERSTER, O. (1931), *Lancet*, **2**, 309.
FULTON, J. F. (1933), *Proc. Calif. Acad. Med.*
——(1936), *Proc. Inst. Med. Chicago*, 11.
HINES, M. (1944), "The Precentral Motor Cortex." Univ. Illinois Press, Ch. 18.
LASHLEY, K. S. (1937), *Arch. Neurol. Psychiat.*, **38**, 371.
——and CLARK, G. (1946), *J. Comp. Neurol.*, **85**, 223.
LIDDELL, E. G. T., and PHILLIPS, G. C. (1944), *Brain*, **67**, 1.
LLOYD, D. P. C. (1941), *J. Neurophysiol.*, **4**, 525.
MARSHALL, C. (1934), *Arch. Neurol. Psychiat.*, **32**, 778.
METTLER, F. A., METTLER, C. C., and CULLER, E. A. (1935), *ibid.*, **34**, 1238.
VON MONAKOW, C. (1917), *Ergebn. Physiol.*, 206.
RAMSAY HUNT, J. (1917), *Brain*, **40**, 58.
RANSON, S. W. (1936), *Arch. Neurol. Psychiat.*, **35**, 1399.
SIMONS, A. (1923), *Ztschr. f. d. ges. Neurol. u. Psychiat.*, **80**, 499.
TOWER, SARAH (1935), *Brain*, **58**, 238.
——(1936), *ibid.*, **59**, 408.
——(1940), *ibid.*, **63**, 36.
——(1944), The Precentral Motor Cortex, Univ. Illinois Press, Ch. 6.
WALSHE, F. M. R. (1915), *Brain*, **37**, 269.
——(1919), *ibid.*, **42**, 1.
——(1923), *ibid.*, **46**, 1.
——(1927), *ibid.*, **50**, 377.
——(1942a), *ibid.*, **65**, 48.
——(1942b), *ibid.*, **65**, 409.
——(1943), *ibid.*, **66**, 104.
——(1946), On the Contribution of Clinical Study to the Physiology of the Cerebral Motor Cortex, Victor Horsley Lecture, Livingstone, Edinburgh.
——(1947), *Brain*, **70**, 93.
——, and ROBERTSON, E. G. (1933), *ibid*, **56**, 40.
——, and HUNT, J. H. (1936), *ibid.*, **59**, 315.

Notices of Recent Publications.

Sensory Mechanisms of the Retina. By Ragnar Granit. Oxford University Press. 1947. Pp. 412, 178 text figs. Price 35s.

Twenty years ago the physiology of vision had reached a stage of very sluggish advance. A great deal of work had been done relating controlled variations in the illuminating stimulus with corresponding alterations in the sensory experience of light in terms of intensity, form and colour. This work was awaiting interpretation. Based upon it, there were several theories of venerable authority but limited application which had been drained of their ability to inspire new lines of approach to the central problem. Ramon y Cajal had exhaustively described the histology of the receptor mechanism of the retina. The photo-chemistry of visual purple had provided, in the course of the fifty years since its discovery, some indication of the means by which this mechanism might be sensitized to light. As yet there was no clear indication of the processes linking such changes in the retina with visual sensations because, although Du Bois Reymond had demonstrated a hundred years ago the negative variation in active nerve fibres, and the resting electrical potential of the eye and Holmgren twenty years later had recorded electro-retinograms in response to illumination of the eye, these results had provided nothing more than confirmation that the retina contained nervous elements whose activity was associated, as was that of all other neurones, with changes in electrical potential.

It was at that stage that there occurred a sensational advance in experimental technique which altered the whole orientation of this subject to which it was applied. Electronic valve amplification provided a combination of sensity with speed of response which made it possible for the first time to record variations in potential due to the activity of single nerve elements. Adrian, who had already used it to analyse the activity of cutaneous sense organs, suggested from his experience of those results the correct explanation of the complex oscillation records obtained so many years earlier from the retina, and went on to record the activity of single receptor units of the retina and of the optic nerve.

Meanwhile Granit, inspired by Sherrington's emphasis upon the numerous parallels between visual phenomena and reflex behaviour, had been working on this subject with psycho-physical methods at Helsingfors and at Oxford. He at once adapted this technique of Adrian and his collaborators and has since been continuously engaged in the same field. This book, completed in 1943, with addenda to 1946, contains a record of his work. Primarily a presentation of the ascertained facts, it is written throughout, in sustained tribute to Sherrington, as a chapter in neuro-physiology rather than as a monograph on vision. He shows how the complex messages received by the sensory cortex have come to be directly related with the activity of individual retinal elements and how such visual experiences as flicker phenomena, dark adaptation, and the perception of brightness and of colour, have

been found capable of interpretation in the general terms of the electrophysiology of all sensory receptors.

Of the theories erected upon this body of observations, two owe their origin to the author himself. Although Perrin had earlier suggested that there might be two distinct types of retina, Granit is responsible (1935) for giving these E- and I- retinæ biological significance; he alone is responsible for the dominator-modulator hypothesis of visual activity. He believes that it is possible to formulate a reasonable electrical theory of the generation of excitation and inhibition in the retina on the basis of electrical changes which are observed to follow stimulation by light. According to this theory, the E- retina is predominantly a rod retina containing essentially the mechanisms for the integration of weak stimuli characteristic of scotopic eye, but making use also of inhibitory processes. It is the retina of all mammals. The I-retina is a cone retina organized for the interpretation of changes in the visual field, of illumination of the area stimulated, of the locus of the field as a whole and of colour. It is the retina of all animals other than mammals. The interest and the value of this conception lies in the fact that it is derived solely from analysis of the electroretinogram and yet fits in well with the requirements of the duplicity theory and with the distribution of different types of retinal receptor in mammals and in other animals.

Granit's dominator-modulator theory attempts to explain the independence of the two fundamental components of visual experience, i.e. brightness and colour. According to this, the dominator system of retinal receptors provides luminosity or brightness. Modulators are so called because they are concerned with modulating this dominant impression of brightness by the addition of colour. The dominator unit is one of broad spectral sensitivity which responds to many wave-lengths, but does not differentiate between them. The modulators have narrow sensitivity ranges in different regions of the spectrum: these enable them to provide sensitive wave-length discrimination. Granit considers that there are enough variations in fibre diameter in the optic nerve to provide a sufficient number of modulator paths. The fact that the chief effect of fatigue by coloured light is a reduction in brightness is easily accounted for upon this theory, but not upon the trichromatic theory.

In this book the author is not concerned to draw attention to the clinical significance of the many facts which he records, but in an appendix on the human electro-retinogram he shows how this can be very easily and simply obtained and claims that it is already a valuable diagnostic aid. Working under standard conditions of near dark adaptation and using a cotton wick electrode making contact with the cornea in the region of the limbus and held into position by a contact lens, reliable records can readily be obtained from the human subject. Of the results of clinical interest to which he refers, two may be indicated. As the rate of interruption of a flickering source of light is increased, the electroretinogram becomes smooth ("indistinguishable from one obtained with steady illumination") at a rate at which the cortex still provides the sensory experience of an obviously flickering light. This may be due to the fact that the electroretinogram is dominated by activity of the rods with their lower fusion frequency, while the sensory cortex may still receive intermittent stimulation from the higher frequencies provided by the cones. Again, it is known that the blocking of the Alpha-rhythm of the electrencephalogram by illumination of the eye occurs after a latent period dependent upon the intensity of the illumination used. Illumination of the eye also provides an oscillating variation in the electroretinogram, and this also occurs after a latent period dependent upon the intensity of the illumination. The investigations of Bernhard indicate that these variations in the blocking time of the Alpha-rhythm of the electrencephalogram are mainly dependent upon changes in the retina, and since the latent period of the

retina is often greatly prolonged in certain pathological changes in the eye itself, it is likely that such changes will have considerable effect upon the activities of the cerebral cortex.

Granit believes that the human electroretinogram may soon become an important method of investigation in the routine practice of every ophthalmological clinic. If this is so, it will provide an interesting contrast with the electrencephalogram because, although much use has been made of the latter for several years in detecting and in localizing lesions of the cerebral cortex, it still awaits reliable interpretation in terms of normal and altered neuronic activity.

Clinical Examination of the Nervous System. By MONRAD-KROHN. Eighth Edition. 1947. H. K. Lewis. Price 16s.

Handbook of Neurological Examination and Case Recording. By D. DENNY-BROWN. 1946. Harvard University Press. (London: Geoffrey Cumberlege.) Price 10s. 6d.

These two manuals, both by title dealing with the same subject, are very different in scope and method. Professor Monrad-Krohn's familiar work has now expanded to 370 pages, an increase of 60 pages over its last issue, while Professor Denny-Brown's modest handbook is but 112 pages in length, and is without illustrations.

The fact is that Monrad-Krohn's book has outstripped its title and has become in many ways a textbook of clinical neurology, and it may be said to have fallen between two stools—it is too lengthy and diffuse for its title, and yet inadequate as a textbook of neurology. Much drastic pruning of matter is called for, and a recasting on more methodical and physiological lines of the chapters dealing with reflexes and the motor system. We know that clinical neurology is more than applied physiology, but nevertheless the careful application of physiological knowledge and principles to the description of normal and abnormal reflex reactions and of motor disorders both simplifies, clarifies and shortens description.

Since the book undertakes clinical description on a large scale, the poverty and unequal character of much of the accounts of the phenomena of epileptic and epileptiform fits, of the two forms of paraplegia, of the nature and form of paralyses in hemiplegia, of the extensor plantar response and of the Argyll Robertson pupil, to take but a few examples, is striking.

A great deal of old and now outdated matter could with advantage be omitted from future editions, and by this means this valuable book could be reduced in size and expense and its usefulness greatly enhanced.

Its unsystematic bibliography is predominantly Scandinavian, that is, it consists largely of references to papers which are inaccessible to, and unreadable by, readers outside Scandinavia.

Denny-Brown's small handbook may be said to fulfil the purposes of an account of neurological examination adequately, without going beyond its stated role, and it has a chapter on special investigations that is admirable in conciseness. It may be very warmly recommended to the student of neurology. It has two disadvantages only, and these are of production. It is printed in "artificial typewriting", which is trying to read, and its price in this country is half a guinea. This is excessive and must militate against that circulation the book deserves and the promotion of neurological studies requires.

Further Studies in Encephalography. By E. GRAEME ROBERTSON, M.D., F.R.C.P., F.R.A.C.P. 1946. Melbourne. Macmillan and Co. Ltd. Pp. 104+x. Price 35s.

This monograph is largely concerned with the factors which control filling of the ventricular and subarachnoid spaces during lumber pneumoencephalography. These have been investigated in the living patient, in the cadaver and in models of varying complexity designed to reproduce the physical properties of the cerebrospinal fluid pathways. When the head is flexed so that the foramen of Monro lies at a horizontal level below that of the termination of the aqueduct filling of the lateral ventricles occurs and is attributed by the author to expansion of these centres occasioned by the local rise in pressure in the third ventricle when it is filled with gas. This increase in pressure causes a flow of fluid and later gas from the third into the lateral ventricles. When the head is extended filling of the ventricles occurs more readily (although subarachnoid filling is added) and is thought to be due to both ventricular dilatation as above and a gravitational downflow of fluid from the lateral ventricles. The author considers that since ventricular filling occurs as readily in the cadaver as in the living patient a fluctuating intraventricular pressure occasioned by changes in vascular tension can play no part in filling of the ventricles. It should be noted, however, that intracranial pressure falls very considerably after death and in the cadaver sitting upright will therefore be extremely low. This should make ventricular filling especially easy and therefore the importance of a pulsatile intraventricular pressure in allowing ventricular filling in the living patient cannot be dismissed. Nor can it be said that any model—no matter how carefully constructed—can reproduce with exactitude the physical properties of the complex cerebrospinal fluid pathways.

Detailed information concerning the effect of posture on ventricular filling is given and the author's technique is fully considered, together with his opinions upon the preparation of the patient, anæsthesia, and the choice of gas to be injected. The good visualization of the intracerebral spaces which follows his careful technique is indicated by the fact that failure to fill them occurred in only 2 per cent. of cases.

The demonstration of the various intracranial spaces besides the ventricles receives full consideration and the findings in hydrocephalus, developmental abnormalities and in certain pathological conditions are considered. The author suggests that he is prepared to do a lumbar pneumoencephalogram in the presence of raised intracranial pressure and that craniotomy may subsequently be delayed for some days. Many neurosurgeons would feel that when there is intracranial hypertension ventriculography is a much safer procedure and should be followed by immediate exploration. The displacement of the septum pellucidum away from the side of an atrophic lesion of the hemisphere is described as a frequent occurrence—which will come as a surprise to many.

This book is beautifully produced and illustrated, is easily readable and contains an account of much thoughtful work in the field of pneumoencephalography. It should be read by all interested in the subject.

The Principles of Neurological Surgery. By LOYAL DAVIS. Third Edition. London. Henry Kimpton. Pp. 540. Price 37s. 6d.

A new edition of this textbook is very welcome. It is one of the few of its kind available and its author's desire to provide the medical student and practitioner with easily assimilable information on the field of neurosurgery is more than realized.

Indeed, the information provided should be invaluable to the neurological house surgeon and the book should also have a strong appeal to those working for higher surgical degrees.

Neurological examination and its anatomical and physiological basis is first briefly discussed. Then follows a good account of head injuries. Intracranial tumours are fully considered but only one-fifth of the book is devoted to them—an indication of the increasing scope of neurosurgery. Injuries and compression of the spinal cord also receive close attention and there is a full discussion of peripheral nerve injuries. Other shorter sections deal with pain, lesions of the cranial nerves and the skull, the surgery of the autonomic system, epilepsy, hydrocephalus and spina bifida.

The book is extremely readable and well produced with many illustrations. In view of the avowed aim to produce a work for practitioners and students there is a danger in its continued growth. It might be that with this end in view certain sections might be condensed without any reduction in their value. As examples the mode of testing the function of individual muscles and the detailed account of the findings in lesions of the individual peripheral nerves could be omitted. Among the few points that are likely to be criticized may be mentioned the definition of cerebral fungus and cerebral hernia, the omission of mention of the importance of a tentorial pressure cone in the production of Hutchinson's pupil and the statement that when the diagnosis of a lumbar disc protrusion has been made rest in bed cannot help and the only logical treatment is removal of the protrusion.

However, it would be wrong to lay too much stress on such criticisms of minor points for the book is an excellent one and likely to retain its popularity for a long time.

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